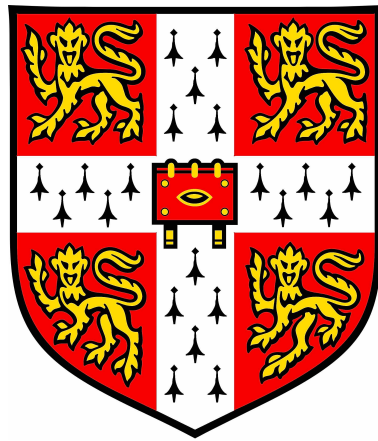


3D ANALYSIS OF THE HIP JOINT FOR THE PREDICTION OF OSTEOARTHRITIS



A THESIS PRESENTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

By

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March 2019

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Abstract

Hip osteoarthritis is an increasingly important cause of morbidity in the ageing population causing pain, disability and loss of function through joint failure. It has an estimated lifetime risk of 25%. While the contribution of skeletal morphology to disease is now established, the lack of imaging biomarkers that can reliably predict osteoarthritis development is limiting. Novel biomarkers for clinically relevant hip osteoarthritis are needed particularly methods to identify patients who are destined for total hip replacement (THR) surgery and who might benefit from novel interventions. The chosen techniques studied here involved 2D and 3D measures of hip cortical bone structure from routine clinical computed tomography (CT) scans of patients to predict clinically-relevant hip osteoarthritis. Outside the research environment, clinical practice and trials still use simple 2D outcome measures from radiographs. Clinical diagnosis and surgical decision making therefore rely on combinations of poorly-defined disease signs and symptoms and controversially, 2D radiographic imaging. Such methods overlook key 3D disease features. In many osteoarthritis guidelines, clinicians are now advised to avoid imaging altogether.

This work asked three important research questions concerning hip osteoarthritis.

1. Does imaging have clinical utility in managing patients with hip pain, and in particular are hip radiographs effective in predicting THR?
2. Does 3D imaging using clinical CT have clinical utility in predicting THR, and is there a 3D phenotype of bone thickening associated with eventual THR?
3. Is the 3D bone thickening associated with hip osteoarthritis an inevitable consequence of ageing?

In order to answer these, CT cortical thickness data was acquired from two population based studies; one in only older men and women from the Age, Gene/Environment Susceptibility-Reykjavik (AGES) Study in Iceland and the other from the Mindways study acquired from 11 healthcare centres around the USA, of women aged 20-97 years.

CT scans were coupled with new image analysis techniques called 3D cortical bone thickness mapping, statistical parametric mapping and disease feature distribution mapping. Recently it was hypothesised that focal bone thickening in regions of the hip cortex would be associated with eventual hip joint replacement and radiological progression of osteoarthritis features.

Combining hip pain, radiographic osteoarthritis grade and CT gave excellent discrimination of THR (0.90;0.85,0.95). Conversely, hip pain was a poor to marginal predictor (AUC=0.70; 95%CI 0.62,0.78). The AUC for radiographic Kellgren and Lawrence (K&L) osteoarthritis grade alone was 0.87(0.81,0.92), irrespective of hip pain, with single mJSW being a reasonable discriminator (0.80;0.73,0.87). Osteoarthritis was also associated with a CT-defined crescent of femoral head surface bone thickening (Odds Ratio for THR; 5 per SD thicker; 5.0(3.2,7.7), 0.85(0.79,0.91)). In a typical clinical presentation with hip pain, all of the imaging parameters measured ranged from good to excellent in terms of clinical utility.

Imaging unequivocally predicted THR for osteoarthritis, whether or not pain had become apparent. Contrary to current guidelines, images of patients with hip pain have good to excellent clinical utility for selecting surgically-relevant presentations. If patients with definite hip pain had definite radiological osteoarthritis, 85% went on to THR within 3 years.

Thesis Overview

In this study my research aims are to establish phenotypes of hip structure that are predictive of osteoarthritis as potential novel biomarkers.

I aim to discover the clinical utility of existing 2D radiographic and novel 3D CT measures in managing patients with hip pain by testing the following hypotheses.

1. 2D imaging will have clinical utility in predicting hip replacement in those with hip pain.
2. The 3D distribution of cortical bone thickness around the proximal femur will predict hip replacement in those with hip pain.
3. The 3D printed model of the SPM osteoarthritis ROI result will help with the understanding of OA disease features.
4. The distribution of cortical bone in the femoral head will become “osteoarthritic” with ageing which will manifest as regional “thickening”.

Key Questions

The clinical utility of any imaging biomarkers is paramount. How will it be useful among patients presenting with osteoarthritis signs and symptoms in the clinic? Is imaging reliably associated with pain? Does it reliably predict hip replacement? For this, predictive diagnostic methodology including receiver operating characteristic analysis will be needed.

Turmezei et al published a method for manual classification of hip osteoarthritis, describing radiological CT features related to clinical osteoarthritis [1, 2]. My premise is that the systematic global evaluation of subchondral thickening of the femoral head may be the single most important factor of those measured (such as cysts, osteophyte load and joint space narrowing), because subchondral thickening seems to precede the damage in animal models of osteoarthritis.

Dedication

I dedicate this thesis to my loving parents, you have always supported me and been there, through thick and thin. I could not have achieved a fraction of what I have in this world without your countless sacrifices, endless guidance and love. Thank You!

Vera & Sergei

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the preface and specified in the text.

I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University of similar institution except as declared in the preface and specified in the text.

Unless otherwise stated (in the caption text) all images, figures and photographs in this thesis were drawn and created by myself using specialist imaging software.

The thesis does not exceed the prescribed limit of 60,000 words.

Ilya S. Burkov

Date

Acknowledgements

This PhD was carried out in Addenbrooke's Hospital, Department of Medicine, University of Cambridge from 2014 to 2018. Part of the thesis was carried out in a collaboration with The Icelandic Heart Association, in Reykjavik, Iceland. The study was funded by National Institutes of Health contract N01-AG-012100, the National Institute on Aging Intramural Research Program, Hjartavernd (the Icelandic Heart Association), the Althingi (the Icelandic Parliament) and the Adrian J. Crisp Studentship which funded my PhD.

I owe my deepest gratitude to my supervisor, my friend and role model, Dr. Kenneth Poole, for his inspiring guidance, endless support and for sharing his expertise from the first day to the final day of this PhD. I admire his dedication to his patients and the entire bone research team. It has been an absolute privilege to work in his research group and wish him all the success in future research endeavours. I would also like to extend special thanks to all of the individuals in the Bone Research Lab for their help and advice with the numerous challenges I faced. In particular Doctors Fjola Johannesdottir, Linda Skingle, Simona D'Amore, Hiroshige Sano and senior research nurse Karen Blesic. The team in Iceland who welcomed me for 8 months of imaging analysis, Sigurdur Sigurdsson and Professors Thor Aspelund, Helgi Jonsson and Vilmundur Gudnason.

I would like to acknowledge Doctors Graham Treece and Andrew Gee at the Cambridge University Engineering Department, who helped me understand the cortical bone mapping technique and wrote the original scripts (as described in Appendices B and C) and assisted with the analysis of data as well as with the post-registration processes. Doctors Tom Turmezei and Tristan Whitmarsh have both been crucial throughout my PhD project in particular using their Matlab programming knowledge (as described in Appendix D) to help create 3D print-ready volumes.

A special thanks to Doctors Stephen Kaptoge, and Stephen Sharp for their assistance with statistical analysis of the AGES data.

Publications And Conferences

Throughout the past 4 years our work with the AGES Study has travelled to numerous specialised conferences for a variety of both oral and poster presentations.

Publications

As of March 2019 a journal paper entitled “*Predicting THR For Symptomatic Osteoarthritis Using Radiographs of Pelvic Clinical Computed Tomography; A Prospective Case-Control Study*” was submitted to Arthritis Care & Research, and is at present out for peer review.

Conferences

- **August 2018 - Plenary Poster Session**

American Society for Bone and Mineral Research (ASBMR)

- **July 2018 - Poster Presentation**

International Workshop on Osteoarthritis Imaging (IWOI)

Our abstract was 1 out of the 68 abstracts submitted selected for a poster presentation.

- **April 2018 - Poster Presentation**

*World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
(WCO-IOF-ESCEO)*

Our abstract was 1 out of the 1513 abstracts submitted selected for a poster presentation.

- **August 2017 - Plenary Poster Session**

American Society for Bone and Mineral Research (ASBMR)

Our abstract was 1 out of 1310 abstracts submitted selected for a plenary poster session.

- **July 2016 - Poster Presentation**

Medical Imaging Summer School (MISS)

Our abstract was 1 out of the 62 abstracts submitted selected for a poster presentation.

- **June 2016 - Oral Presentation**

International Workshop on Osteoarthritis Imaging (IWOI)

Our abstract was 1 of 12 abstracts selected for an Oral Presentation (from 70 abstracts submitted).

- **June 2016 - Oral Presentation**

European League Against Rheumatism (EULAR)

Our abstract was 1 of the 7.67% of chosen abstracts, from 4109 submitted.

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Nomenclature

<i>2D</i>	Two-dimensional
<i>3D</i>	Three-dimensional
<i>AAC</i>	Arthritis Alliance Of Canada
<i>ACI</i>	Autologous Chondrocyte Implantation
<i>ACT</i>	Autologous Chondrocyte Transplantation
<i>AGES</i>	Age, Gene/Environment Susceptibility-Reykjavik Study
<i>AHRQ</i>	Agency For Healthcare Research And Quality
<i>AP</i>	Anterioposterior
<i>AUC</i>	Area Under The Curve
<i>BMD</i>	Bone Mineral Density
<i>BMI</i>	Body Mass Index
<i>CBM</i>	Cortical Bone Mapping
<i>CBMD</i>	Cortical Bone Mineral Density
<i>CFPC</i>	Centre for Effective Practice Guidance Tool
<i>CI</i>	Confidence Interval
<i>CMYK</i>	Cyan, Magenta, Yellow, and Key
<i>COX</i>	Cyclo-Oxygenase
<i>CT</i>	Computed Tomography
<i>CTh</i>	Cortical Thickness
<i>DALY</i>	Disability-Adjusted Life Year
<i>DEFT</i>	Driven Equilibrium Fourier Transform
<i>DICOM</i>	Digital Imaging and Communications in Medicine
<i>DRR</i>	Digital Reconstructed Radiographs
<i>DXA</i>	Dual-Energy X-Ray Absorptiometry
<i>ECTD</i>	Endocortical Trabecular Density
<i>EULAR</i>	European League Against Rheumatism Guideline

<i>FAI</i>	Femoacetabular Impingement
<i>FDA</i>	Food And Drug Administration
<i>FEM</i>	Finite Element Modelling
<i>FID</i>	Free Induction Decay
<i>GCDR</i>	Greatest Common Divisor
<i>GI</i>	Gastrointestinal
<i>GLM</i>	General Linear Model
<i>HA</i>	Hyaluronic Acid
<i>HOAMS</i>	Hip Osteoarthritis MRI Scoring System
<i>HR</i>	Hazard Ratio
<i>HR – pQCT</i>	High Resolution pQCT
<i>HU</i>	Hounsfield Unit
<i>IQR</i>	Interquartile Range
<i>JSN</i>	Joint Space Narrowing
<i>JSW</i>	Joint Space Width
<i>K&L</i>	Kellgren And Lawrence
<i>LCM</i>	Least Common Multiple
<i>MDCT</i>	Multi-Detector Computed Tomography
<i>MHz</i>	Megahertz
<i>mJSW</i>	Minimum Joint Space Width
<i>MRI</i>	Magnetic Resonance Imaging
<i>MSC</i>	Mesenchymal Stem Cell
<i>mSv</i>	Millisievert
<i>MTC</i>	Magnetisation Transfer Contrast
<i>NAV</i>	Voltage-Gated Sodium Channel
<i>NHS</i>	National Health Service
<i>NICE</i>	National Institute For Health And Clinical Excellence
<i>NIH</i>	National Institutes Of Health
<i>NJR</i>	National Joint Registry
<i>NLR</i>	Negative Likelihood Ratio
<i>NMR</i>	Nuclear Magnetic Resonance
<i>NOGG</i>	National Osteoporosis Guideline Group
<i>NPV</i>	Negative Predictive Value
<i>NSAID</i>	Non-Steroidal Anti-Inflammatory Drug

<i>OA</i>	Osteoarthritis
<i>OMERACT</i>	Outcome Measures In Rheumatology
<i>OP</i>	Osteoporosis
<i>OR</i>	Odds Ratio
<i>PICO</i>	Population Intervention Comparator Outcome
<i>PLR</i>	Positive Likelihood Ratio
<i>PPV</i>	Positive Predictive Value
<i>pQCT</i>	Peripheral Quantitative Compound Tomography
<i>PROM</i>	Patient Reported Outcome Measure
<i>QCT</i>	Quantitative Computed Tomography
<i>QIBA</i>	Quantitative Imaging Biomarkers Alliance
<i>RA</i>	Rheumatoid Arthritis
<i>RCS</i>	Royal College Of Surgeons
<i>RF</i>	Radio-Frequency
<i>RMSE</i>	Root Mean Square Error
<i>ROC</i>	Receiver Operating Characteristic
<i>ROI</i>	Region Of Interest
<i>ROM</i>	Range Of Motion
<i>SD</i>	Standard Deviation
<i>SDM</i>	Statistical Deformation Modelling
<i>SLR</i>	Systematic Literature Review
<i>SPECT</i>	Single Photon Emission Computed Tomography
<i>SPM</i>	Statistical Parametric Mapping
<i>ST</i>	Slice Thickness
<i>STL</i>	Standard Tessellation Language
<i>TDT</i>	Thomas D Turmezei
<i>TE</i>	Echo Time
<i>THR</i>	Total Hip Replacement
<i>vBMD</i>	Volumetric Bone Mineral Density
<i>VMRL</i>	Virtual Reality Modelling Language
<i>WOMAC</i>	Western Ontario and McMaster Universities

3D Analysis Of The Hip Joint For The Prediction Of Osteoarthritis

Chapter 1

Hip Joint, Bone And Osteoarthritis

1.1 Introduction

This chapter provides a detailed, yet concise overview of the hip joint, the synovial joint structure and the cells that make up bones. It introduces anatomical and physiological information necessary to understand what effect a disease (its symptoms, signs and diagnosis) such as osteoarthritis (OA) has on joint anatomy.

1.2 The Hip Joint In Health And Osteoarthritis

The hip joint is a multiaxial synovial ball and socket joint that consists of the head of the femur and the acetabulum of the pelvis, see *Figure 1.1*. It represents the articulation of the bones of the lower limb and the axial skeleton. It is not only designed for stability and weight bearing but also provides a large articulation area for all essential movement in everyday activities such as: standing, walking and basic leg rotation.

The hip joint is an integral part of daily activities such as sitting, walking and running. The specific anatomy and bio-mechanics of the hip joint is the consequence of evolution and constant bipedal gait. The anatomy of the acetabulum and femoral bone ensures hip stability throughout a wide range of motion. Any abnormality in this precise and delicate anatomy can lead to potential instability and/or impingement within the hip joint. This in turn becomes a risk factor for the development of osteoarthritis. The main forces that act on the hip joint and the muscles around the hip are gravitational forces. Depending on the activity, the hip may be subjected to a peak force of up to eight times a person's body

weight.[3] This makes the hip joint especially prone to “wear and tear”. The hip joint is said to be the third most susceptible (after hand and knee) joint to develop osteoarthritis.[4–7]

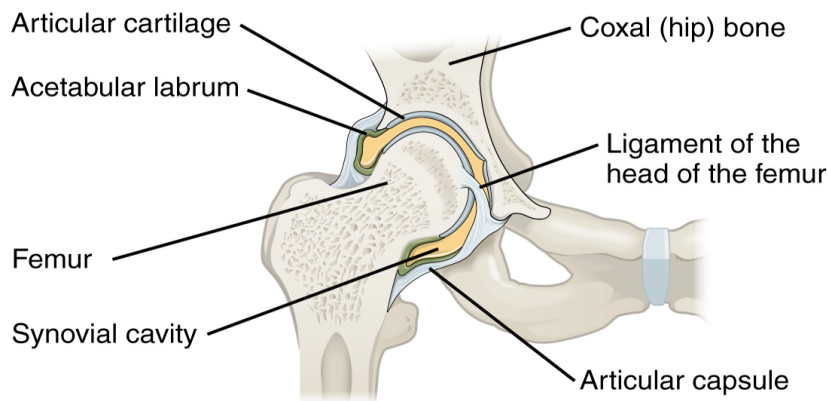


Figure 1.1: Right Hip Joint Anatomy

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The rounded head of the femur, which sits within the concavity of the acetabulum is entirely covered by hyaline cartilage with the exception of a small area known as the fovea capitis femoris. The ligament of the head of the femur (ligamentum teres) spans between capitis femoris and the acetabulum. The hip joint capsule is lined by the synovium, which produces synovial fluid that nourishes the cartilage and lubricates the joint.

The acetabulum is the part of the pelvis formed where three bones (ischium, ilium and pubis) merge. At the centre of the acetabulum is a non-articulating surface known as the acetabular fossa. This part of the acetabulum is not covered by hyaline cartilage and connects to the ligament of the femoral head. The cartilage of the acetabular surface is thickest at the periphery whereas cartilage of the femoral head is thickest on the medial-central surface. The acetabulum is further deepened by the acetabular labrum, a fibrocartilaginous collar attached to the outer margin of the acetabulum. It expands the depth of the joint increasing its stability and positioning.

The surrounding articular joint capsule is robust and can accommodate a wide range of movement. Ligaments arise from the pelvic bones, at the margins of the acetabulum, and attach to the femur at the base of the neck, see *Figure 1.2*. The ligaments are the iliofemoral ligament, pubofemoral ligament, and ischiofemoral ligament, all of which are arranged in a spiral fashion around the head and neck of the femur. The ligaments are tightened by extension at the hip, therefore they pull the femoral head tightly into the acetabulum when in the upright, standing position. These ligaments stabilise the hip joint and allow one to maintain an upright standing position with minimal muscle contraction preventing the

hyperextension of the hip as well as excessive abduction.

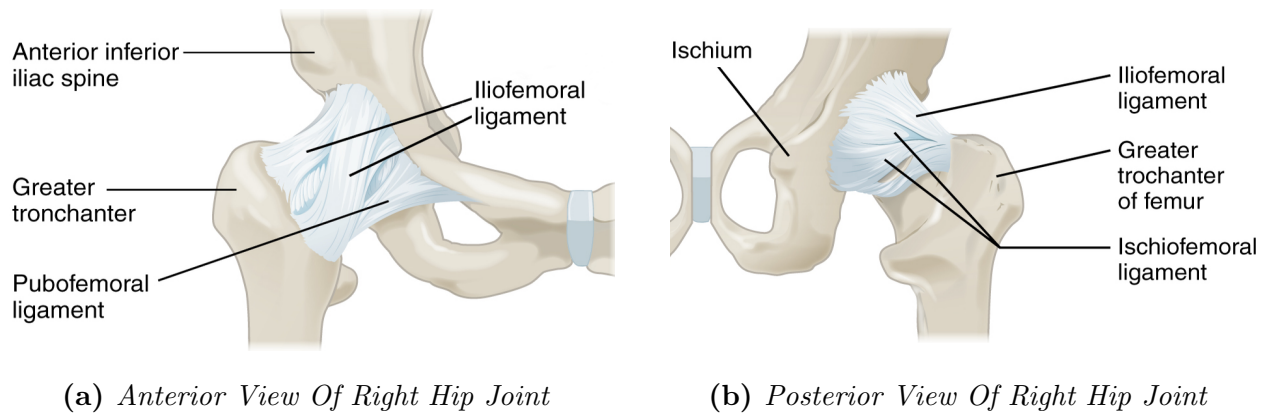


Figure 1.2: Ligaments Of The Hip Joint

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The hip joint capsule is strengthened and reinforced by three ligaments (bands of tough, flexible fibrous connective tissue):

- Anteriorly and superiorly, see *Figure 1.3* by the iliofemoral ligament which connects the anterior, inferior iliac spine and the acetabular rim to the femoral intertrochanteric line (it is the strongest of the femoral ligaments).
- Inferiorly and anteriorly the pubofemoral ligament arises from the obturator crest and the superior ramus of the pubis and blends with the capsule and the medial part of the iliofemoral ligament.
- The ischiofemoral ligament connects the ischial part of the acetabular rim to the neck of the femur.

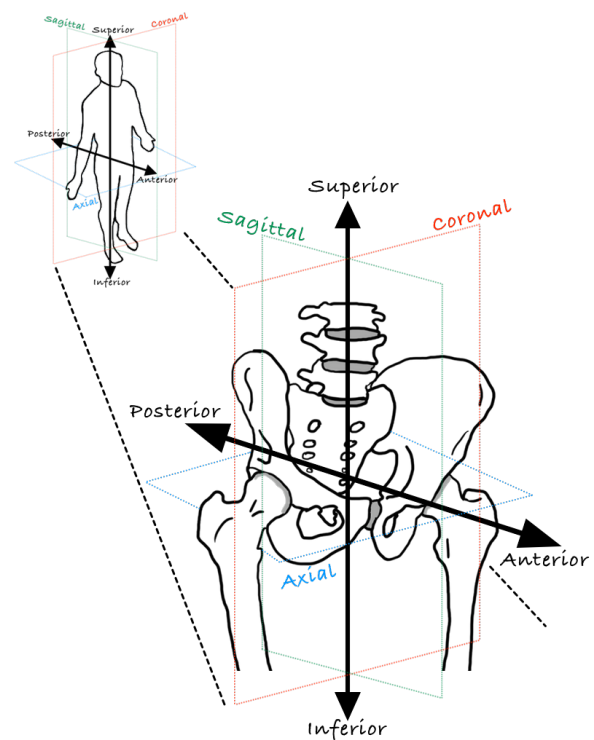
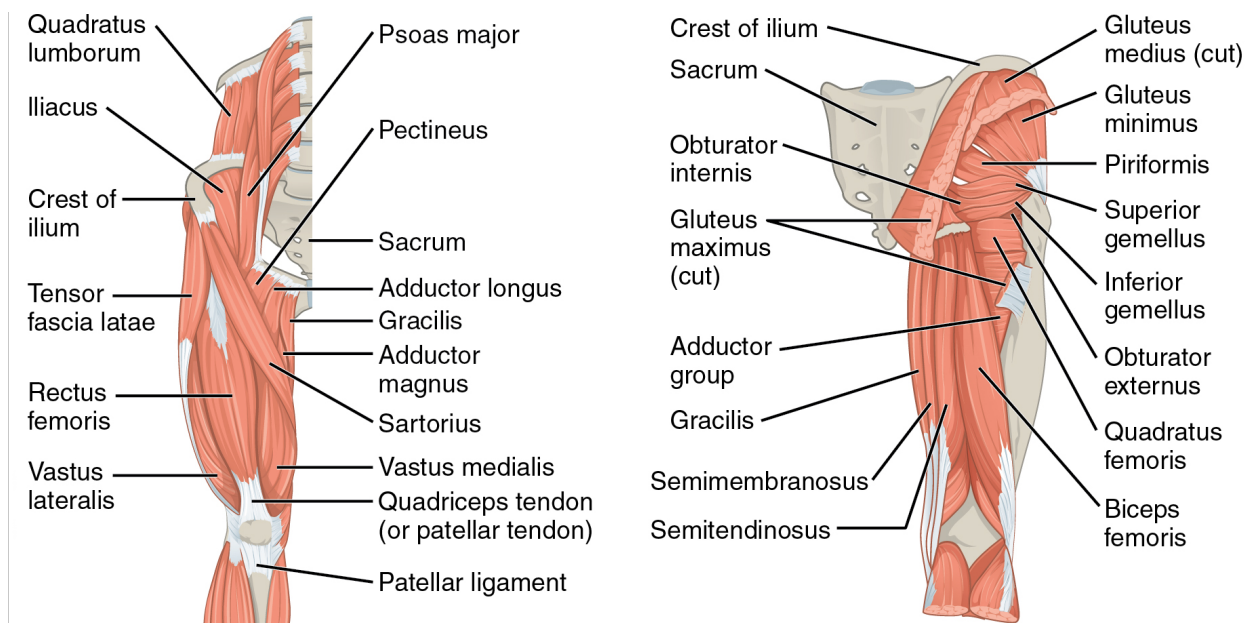


Figure 1.3: Common Anatomical Directions And Radiological Planes

A lot of force is needed to move the femur, hip and legs so the muscles of the hip generally tend to be large and powerful, see *Figure 1.4*. Anterior muscles of the femur extend the lower leg but also assist with the flexing of the thigh. Posterior muscles of the femur flex the lower leg but also assist with the extension the thigh. The gluteal and thigh muscles adduct, abduct, and rotate the thigh and the lower leg. The gluteus maximus, the piriformis, obturator internus, obturator externus, superior gemellus, inferior gemellus, and quadratus femoris are responsible for rotatating the femur at the hip. The adductor longus, adductor brevis, and adductor magnus are responsible for the rotation of the thigh both medially and laterally. The adductor longus flexes the thigh, whereas the adductor magnus extends it and the pectineus also adducts and flexes the femur at the hip. The medial muscles are responsible for adducting the femur at the hip.



(a) *Anterior View Of Pelvic And Thigh*

Muscles Of The Right Leg

(b) *Posterior View Of Pelvic And Thigh*

Muscles Of The Right Leg

Figure 1.4: Muscles Of The Pelvis And Thigh

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Combined, these muscles allow for hip rotation in multiple planes. Flexion and extension (sitting down), internal and external rotation (twisting actions), and abduction and adduction (inward and outward motion of the hip in cross legged actions).

1.3 Synovial Joint Structure

Basic structure of a synovial joint consists of two opposing units of subchondral bone with overlying articular cartilage interposed by a layer of synovial fluid, see *Figure 1.5*.

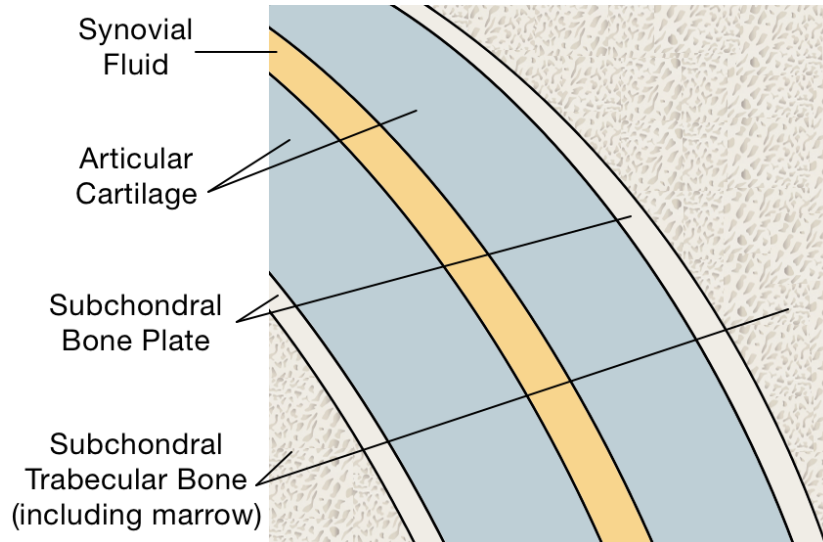


Figure 1.5: Structural Representation (Not To Scale) Of A Typical Synovial Joint

Synovial Fluid

Synovial fluid is clear and its viscosity decreases causing it to thin under shear strain. This “thixotropic” property means that it becomes more elastic as the rate of joint movement increases. As forces are added to a joint, synovial fluid is squeezed out from between opposing joint ends and the force is resisted by the tenacity of the fluid itself ensuring that any friction produced by weight or movement will occur with the fluid rather than between the cartilage surfaces of the bone joints. Synovial fluid is very similar to blood plasma except for the fact that it does not contain fibrinogen or prothrombin and so is unable to clot. The most important component of synovial fluid is a substance called sodium hyaluronate (secreted by the synovocytes) however it also contains mucin, albumin, fat, epithelium, and leukocytes.[8, 9] A typical hip joint contains very little synovial fluid (9.5-4ml).[10] Synovial fluid is responsible for a number of different functions at the same time. Synovial fluid creates a separation area to keep joint bones apart (protecting their cartilage coverings from damage and wear), it absorbs shock, it lubricates the joint helping it move and work without friction and it also responsible for nourishing the avascular cartilage.[11] Norris et al. has shown that when a joint is injured, synovial fluid volume may increase as much as 10-20 times. As the volume of synovial fluid volume increases, hyaluronate

decreases and as this decrease occurs the viscosity of synovial fluid also decreases. It is said that the excess accumulation of synovial fluid volume itself does not cause pain, but it is the speed with which it forms.[12] Blau et al. claimed that as much as 100ml synovial fluid can be extracted from a joint without causing much pain, while a 15ml increase may cause excruciating pain if formed rapidly following a trauma.

Articular Cartilage

Articular cartilage is a thin covering (1-3mm) on the ends of bones that creates moving surfaces of synovial joints.[13, 14] Articular cartilage functions as a shock absorber and reduces friction between bones inside a joint. The articular cartilage covering the subchondral bone plate (of the femur and acetabulum bone) is a specific type known as hyaline cartilage. Radiographic assessment of cartilage in non-osteoarthritis hips has shown that cartilage thickness on the acetabular and femoral sides is not identical. As mentioned in *Section 1.2*, acetabular cartilage is thicker peripherally than centrally, and femoral cartilage is thinner peripherally than centrally.[15] Articular cartilage consists of fibres, ground substance and cells. The fibres are primarily composed of numerous different long-chained extra-cellular matrix molecules (type II collagen,[16] proteoglycans,[17] glycosaminoglycans[18] and chondroitin sulfate[19]) that are essential for structural integrity. Collagen provides cartilage with necessary tensile strength that ensures smooth gliding of opposing articular surfaces in a bone joint. Type II collagen makes up 55-75% cartilages dry weight.[20] The ground substance consists of proteoglycans and glycosaminoglycans (15-30%) as well as water (70-80%).[21–23] Various glycans present have unique bonds with water molecules that ensure articular cartilage can easily resist and redistribute compressive forces. These molecules are incorporated in an aqueous environment with a relatively small volume (<1% of overall cartilage mass) of cartilage cells called chondrocytes (both collagen and proteoglycans are produced by chondrocytes). The structure of cartilage tissue is relatively simple, and it does not contain nerves or blood vessels. If there is constant compression on articular cartilage there will be a decrease in the diffusion rate of synovial fluid which in turn leads to pressure necrosis and chondrocyte death.[24, 25]

Subchondral Bone Plate

The subchondral bone plate is one of the key structures that is evaluated using imaging in this thesis. The plate is a layer of bone underneath the cartilage in the hip. Subchondral bone is an extension of the already shock absorbing articular cartilage and is also able to absorb some shock. Unlike the avascular layer of cartilage above, subchondral bone has many blood vessels supplying it with all necessary nutrients and oxygen, the vessels also remove any waste products produced. These blood vessels are not only essential for the subchondral bone but provide over half of the hydration, oxygenation, and glucose for the cartilage above.[26]

Subchondral Trabecular Bone

Subchondral trabecular bone, also known as cancellous or spongy bone, is an extremely porous type of bone which is highly vascularised and in young adults contains red bone marrow. The marrow spaces amid the trabecular rods and plates give it the “spongy” appearance. This bone is softer and weaker than cortical bone, but this also makes it more flexible and adaptable to any extra forces that may add pressure to it. The micro-architecture of the subchondral bone adapts to its local environment and this includes any mechanical loading from everyday forces.[27, 28] Both subchondral trabecular bone and the subchondral bone plate contain numerous cells called osteocytes with small cavities known as lacunae, forming a lattice-like matrix network. Blood vessels travel through the harder compact bone to the trabecular bone.

1.4 Structure Of Bone

A human skeleton contains a approximately 42 billion osteocytes interconnected inside a matrix of mineralized collagen fibres. Inside this matrix, hydroxyapatite crystals form to give bone its strength and density, while the collagen fibres provide bone with enough flexibility to not be brittle. Although bone cell numbers are relatively small by tissue volume, they are crucial to the function of bones. The four main types of cells that make-up bone are osteoblasts, osteocytes, osteogenic cells, and osteoclasts, see *Figure 1.6*.

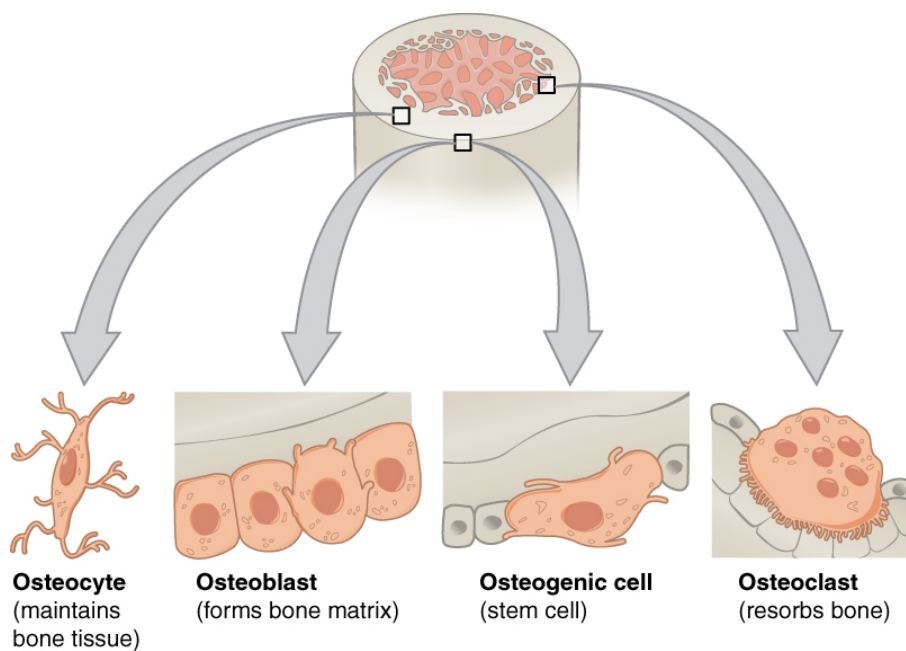


Figure 1.6: Typical Cells That Make Up Bone

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1.4.1 Bone Cells

Osteoblasts (Bone Builders)

Teams of osteoblasts form new bone (osteoid) by secreting collagen matrix particularly during skeletal growth and remodelling. Osteoblasts do not divide but can terminally differentiate into osteocytes. They can also become inactive flat lining cells. The osteoblast becomes trapped within osteoid and changes its morphology to become an osteocyte.

Osteocytes (Bone Maintainers)

Osteocytes are located in a space in the matrix (lacuna) surrounded by mineralized bone tissue. Like osteoblasts, from which they developed, osteocytes cannot divide and lack mitotic activity. They normally communicate with one another via long cytoplasmic processes that extend through channels (canaliculi) within the bone matrix, see *Figure 1.7*.

Osteogenic Cells

Osteogenic stem or “stromal” cells are undifferentiated cells and the only bone cells that are able to do undergo mitosis. Osteogenic cells are normally found in the deep layers of the bone and marrow. They are the cells which differentiate and develop into osteoblasts as and when necessary.

Osteoclasts (Bone Resorbers)

The nature of bone is extremely dynamic and as new tissue is constantly formed, the old, injured or unnecessary bone is dissolved for repair to release more calcium for nutrition. Osteoclasts are the cells responsible for the resorption of bone. They are normally found on bone surfaces and are multinucleated cells that originate from monocyte fusion. Osteoclasts continually break down old bone while osteoblasts continually form new bone and this balance is essential for the healthy reshaping of bone, if any of these processes are disrupted or halt there may be a devastating effect of bone health.

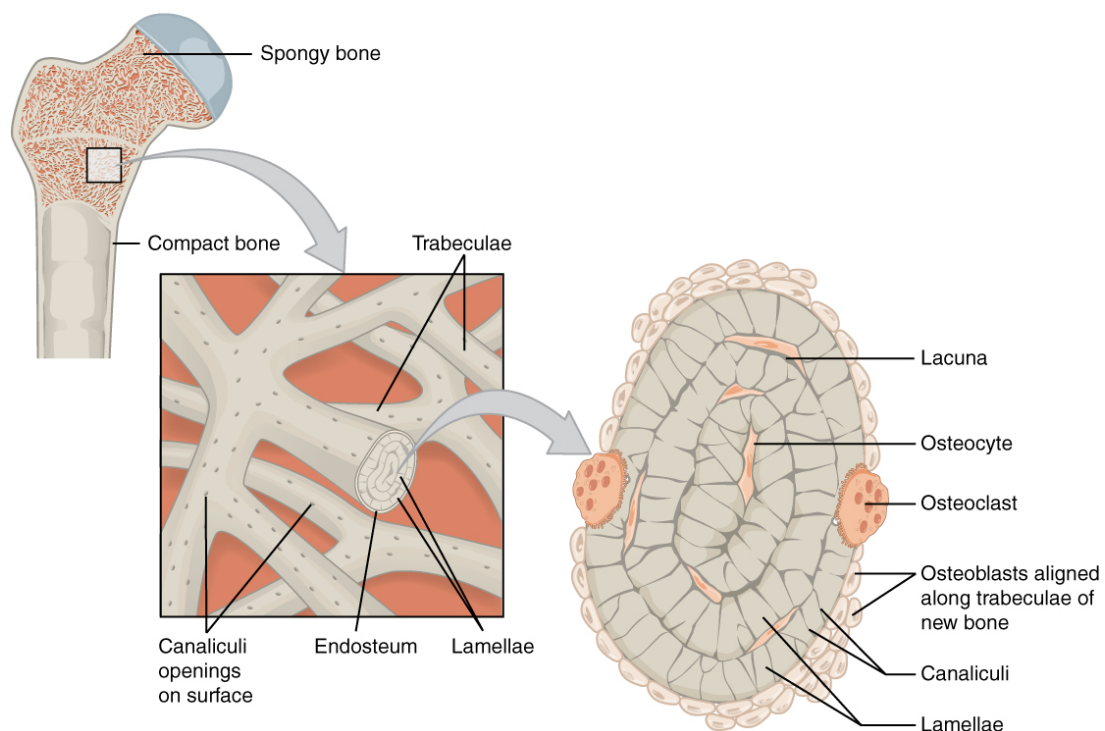


Figure 1.7: Spongy Bone Structure

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1.4.2 Bone Modelling And Remodelling

Formal bone growth, comes to an end at puberty. About 90% of adult bone is formed by the end of adolescence and the continuous process of remodelling begins to occur. A schematic of bone remodelling in cortical and cancellous bone, see *Figure 1.8*. Bone remodelling is responsible for maintaining bone health and ensuring that bones adapt to life and circumstantial changes. As the body ages, bone loses strength and elasticity (due to loss of mineral and matrix volume), therefore it is more likely to fracture and break in older individuals. All bones go through the process of remodelling in order to: mobilise calcium, replace old tissue, adapt to different loads and weight-bearing stress and to repair damaged bone from micro-fractures or micro-damage. As people age and remodelling occurs more and more frequently, all of these repair processes weaken older bone and increase the risk of bone diseases and fractures (especially if bone remodelling doesn't occur quickly enough or is not allowed the opportunity to complete its process before more damage).

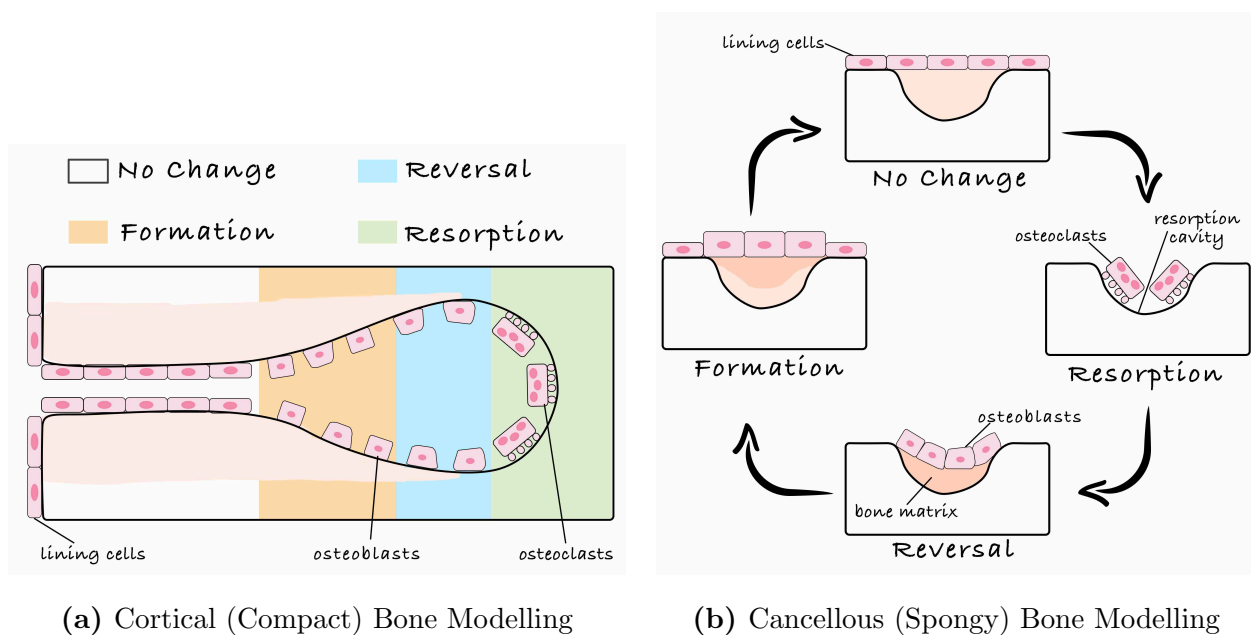


Figure 1.8: Cortical And Cancellous Bone Modelling

1.4.3 Cortical Bone

Cortical (compact) bone, see *Figure 1.9*, forms the hard outer shell of all bones. It is the strongest and densest form of bone in the body. It is a compact bone which makes up nearly 80% of the skeletal mass. Cortical bone is vital to maintain the structure of the body. Its high resistance to torsion and bending makes it ideal for weight bearing. As stress is applied to particular regions of the body, the thickness of cortical bone adapts and varies over time.

Cortical bone is mainly made of osseous tissue. This osseous tissue consists of osteocytes, surrounded by a solid inter-cellular matrix of minerals and protein fibres. Structurally, cortical bone is made of osteons. Osteons are formed at the foetal stage of development when blood vessels and nerve fibres pass through mesenchymal tissue containing osteogenic cells. The ring of bone matrix is formed of these osteogenic cells, known as a lamella. As soon as the lamella has formed, osteogenic cells become known as osteocytes. These osteocytes remain in the osseous tissue in cavities known as lacunae. Canals known as canaliculi, provide osteocytes with nutrients and oxygen from the surrounding blood vessels. During the developmental process, this process repeats itself forming concentric layers of lamellae.

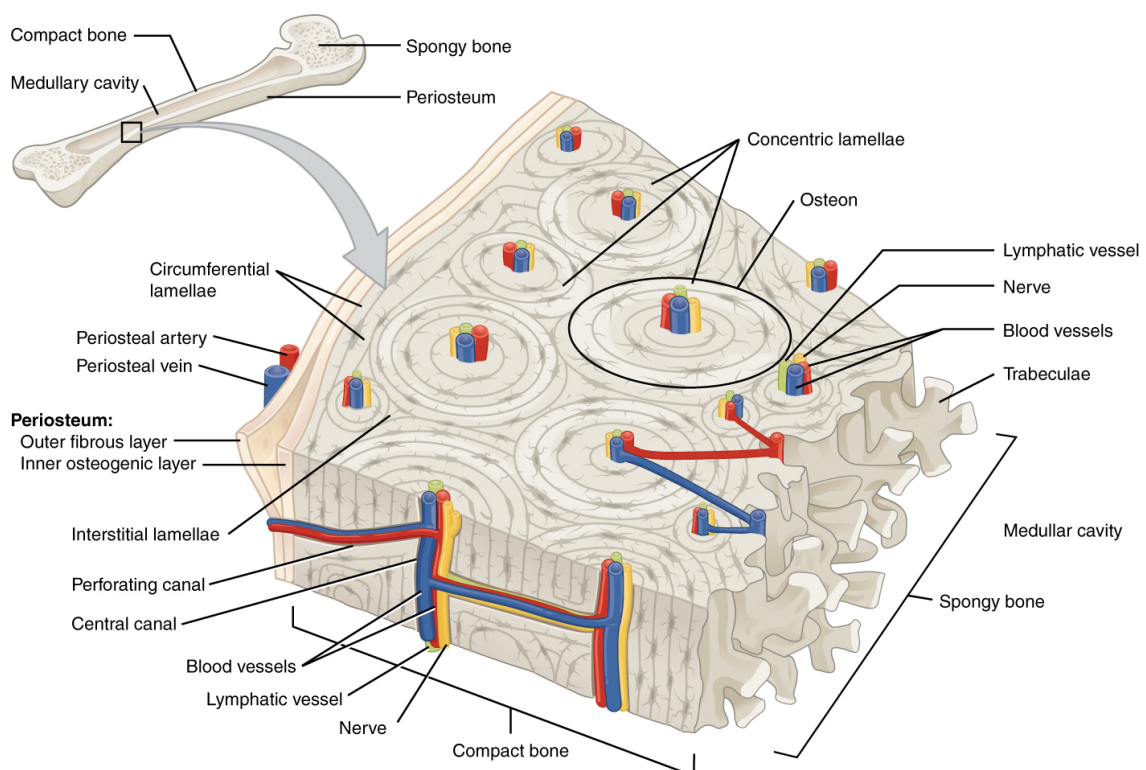


Figure 1.9: Cortical Bone Structure

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1.4.4 Cortical Bone Mapping

Cortical bone mapping (CBM) is a technique that can be used to measure localised skeletal changes from computed tomography (CT) images. CBM can provide detailed measurements with far more accuracy than “simple full width half maximum estimations” from low-resolution QCT data, with good differentiation between thickness, density, and mass. It can detect changes in numerous properties of the bone cortex, with no prior assumptions about the likely location of changes.[29]

The CBM technique has already been used to reveal associations between fracture risk and cortical properties in specific regions of the proximal femur which present feasible therapeutic targets.[30] Where results demonstrated that CBM predicts fracture type better than bone mineral density measurements alone. CBM has been successfully implemented to reveal associations between fracture risk and cortical properties in particular regions of the proximal femur (which present feasible therapeutic targets). CBM has been used to assess the joint space width,[31] which is indicative of cartilage thickness and therefore important in the evaluation of osteoarthritis. CBM measures in men and women have been shown to predict fracture type better than bone mineral density measurements alone. Although most work has been conducted at the femur, CBM has also been shown to measure the vertebral cortex accurately, allowing estimation of osteoporosis treatment responses.

The CBM technique is not limited to only CT data and has been successful in assessing cartilage thickness directly, at the knee using magnetic resonance imaging (MRI).[32] If CT data of the same area was to be used it would have only shown cartilage thickness inferred indirectly from the joint space. CBM however has never been used in a study predicting THR and hip pain and very minimally used to understand how osteoarthritis-prone parts of the femoral head cortex change with age. This is where my study and this thesis comes in. It will address these gaps in the knowledge. It will do so by applying the CBM technique combined with statistical parametric mapping (SPM) on a gathered cohort of participants complete with hip pain data.

1.5 Osteoarthritis Of The Hip

While hip osteoarthritis is typically referred to as a degenerative disease, it actually results in constant new tissue growth, the problem is that it is normally in the form of irregular cartilage and osteophytes,[33] and thus even though there is cartilage growth it is detrimental growth.

In epidemiological surveys the definition of hip osteoarthritis is often based on symptoms, clinical signs, radiological signs or a combination of any of these.[34] In orthopaedics and rheumatology, the definition of hip osteoarthritis is a combination of joint pain, stiffness and radiographic changes such as loss of joint space width, osteophytes, cysts and sclerosis.[35] Typical physical changes that occur in hip osteoarthritis are demonstrated by *Figure 1.10*.

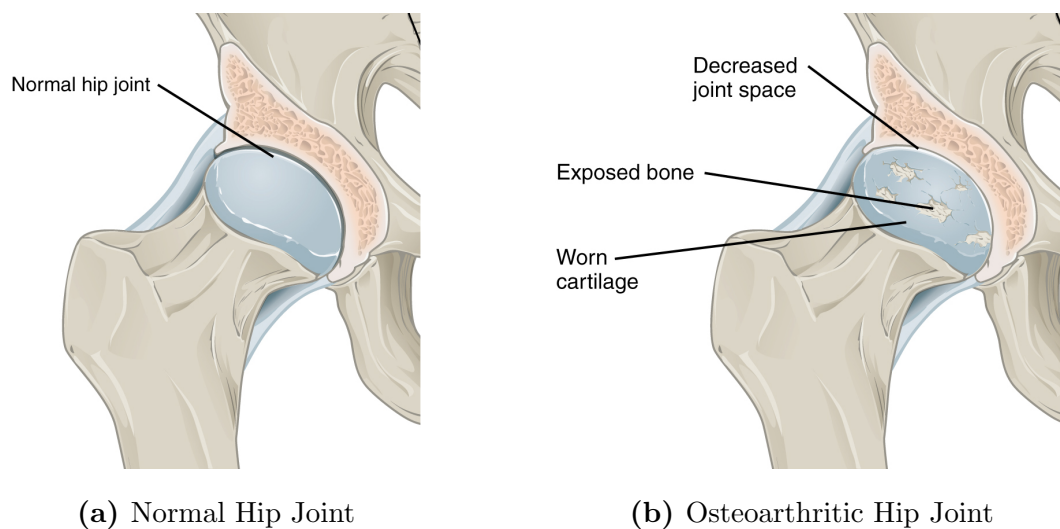


Figure 1.10: Normal vs Osteoarthritic Hip

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When hip cartilage has deteriorated:

- New cartilage may be produced, but the new cartilage cells will grow in irregular, bumpy patterns, rather than smooth. The result is that the femur and pelvic bones rub and grind against one another.
- The bones may produce small, scalloped growths called osteophytes, to compensate for the deteriorated cartilage. In turn, the osteophytes can create even more friction.
- Tendons and ligaments can also be stretched or otherwise compromised in an attempt to compensate for the abnormal joint.

1.6 Osteoarthritis

Osteoarthritis is a progressively degenerative disease of a joint and a major cause of pain and disability in older adults. Not only does it cause damage and loss of hyaline articular cartilage but there is also remodelling of the sub-articular bone, ligaments laxity, osteophyte formation, weakening of the periarticular muscles and synovial inflammation.[36, 37] As the cartilage, which normally cushions the joint by reducing friction (and serves as a “pressure absorber”) becomes damaged, it prevents smooth movement of the joint. Although cartilage may undergo some repair (very minimal) after becoming damaged, the body does not easily regenerate cartilage after it is injured[38, 39] and persistent re-injury is very common.[40] Cartilage damage itself does not cause pain because cartilage does not contain nerve endings that could signal pain to the brain, pain is usually sensed by the bone and other non-cartilage tissues. Osteoarthritis can be a particularly debilitating form of arthritis because it tends to heavily affect load-bearing joints such as the hips and knees (both of which are crucial to maintain normal movement). In 2013 the World Health Organization classified osteoarthritis as the most common condition affecting the musculoskeletal system and one of the fastest increasing global health problems.[41] There has been a 20% increase in cases of arthritis since 2002; of the >54 million US adults (23%) reporting arthritis diagnosed by a doctor, almost 60% are below the usual retiring age.[42] Estimates from the US suggest that hip replacements for osteoarthritis will increase 174% by 2030.[43] Globally, systematic osteoarthritis affects an estimated 18% of women and 9.6% of men over the age of 60, 80% of those with osteoarthritis will have limitations in movement, and 25% cannot perform their major daily activities of life.[44] In economically developed countries, osteoarthritis has been reported in 40% of those 70 years of age and over.[45] Hip osteoarthritis has a radiographic prevalence of 2.3% among women and 1.9% among men over the age of 45 years.[46]

At present, little is known about the pathogenesis of primary osteoarthritis and early detection is very challenging. Surgical interventions for early stage osteoarthritis, such as regenerative treatments,[47] are limited, due in part to the lack of accurate quantification of disease severity and in particular early-stage disease features using current diagnostic imaging methods. This often means that current osteoarthritis treatment is limited to analgesics, weight loss and physical therapy exercises, where appropriate, often until joint damage and pain are serious enough to warrant a total joint replacement. The number of joint replacements has been increasing annually[48] and is likely to continue to increase exponentially,[43]

this will likely be a huge burden for health-care systems around the world not to mention, increased costs for the already stretched health-care economic budgets.

Hip osteoarthritis is central to this thesis, and yet it is hard to reach an acceptable consensus on its definition. The definition of hip osteoarthritis varies throughout studies depending on the research method. Some studies include self-reported osteoarthritis (usually from a questionnaire), radiographic definitions of osteoarthritis (fully explained in *Section 2.2.1*), and symptomatic osteoarthritis.

Cooper et al.[49] define hip osteoarthritis as:

“A clinical syndrome of failure of the joint accompanied by varying degrees of joint pain, functional limitation, and reduced quality of life due to deterioration of articular cartilage and involvement of other joint structures.”

According to the Centers for Disease Control and Prevention (CDC), the lifetime risk of developing symptomatic hip osteoarthritis is 18.5% for men and 28.6% for women.[50, 51] Globally, of the 291 most common conditions,[52] osteoarthritis of the hip and knee were ranked as the 11th highest contributors to global disability and 38th highest in disability-adjusted life years (DALYs) (a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death).[53]

The latest global report mentions that the years lived with disability has increased from 10.5 million in 1990 to 17.1 million in 2010.[54] Cross et al. concluded that with the ageing of the population throughout the world, it is important for health professions to prepare for an exponential increase of people with osteoarthritis requiring health services. Strategies to reduce hip and knee osteoarthritis through primary and secondary prevention programmes will become increasingly important. Improvements in imaging technologies may allow for the development and improvement of treatment strategies in early disease identification by providing detailed assessments of the arthritic joint.

1.6.1 UK Prevalence Of Hip OA And Total Joint Replacement

Arthritis is the biggest cause of pain and disability in the UK.[55] In the UK total hip replacements (THR) for symptomatic osteoarthritis have increased by nearly 200% from 1991 to 2006.[56] Between April 2003 and December 2013 there were a total of 620,400 primary hip replacements performed, principally for osteoarthritis (in 93%). The number of revision operations during the same 10 year was 14,903.[57]

According to data collection done by Arthritis Research UK based on data recorded in an anonymised general practice database, the CiPCA dataset[58] 8.75 million people (33% of the population aged 45 years and over) in the UK have sought treatment for osteoarthritis. They go on to specify that 49% were women and 42% were men aged 75 years and over, suggesting that women are more likely than men to have sought treatment, see *Figure 1.11*.

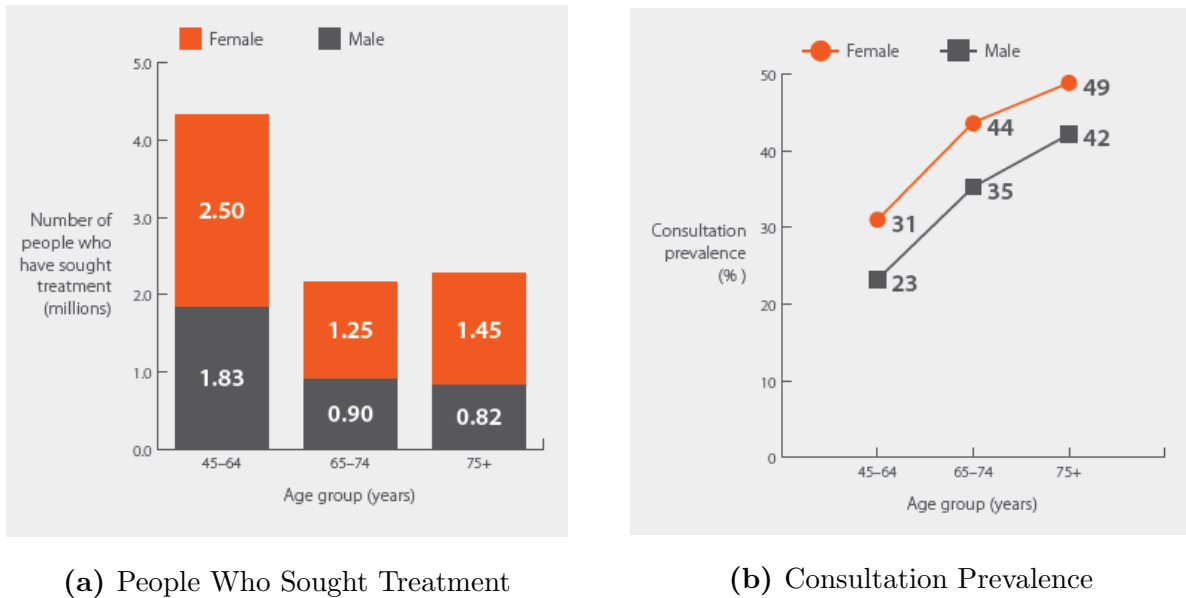


Figure 1.11: Estimated Number Of People In The UK Who Have Sought Treatment For OA, By Gender And Age Group
Used From Arthritis Research UK Information Handbook

The estimated number of people in the UK, aged 45 and over who have sought treatment for osteoarthritis for joint specific sites is summarised in *Table 1.1*. The highest percentage of the population (18%) suffered from knee osteoarthritis, second highest was hip osteoarthritis (8%).

Joint	Percentage of Population (%)	Estimated number (million)
Knee	18	4.7
Hip	8	2.1
Hand & Wrist	6	1.5
Two or more sites	7	1.7

Table 1.1: Commonality of OA in each joint site of people in the UK, aged 45 or over

It is important to get an understanding of how many people in the UK have sought treatments for osteoarthritis of the hip, bearing in mind, however that hip osteoarthritis is challenging

to define and diagnose,[59] and no single diagnostic test of set of clinical criteria have been routinely used in clinical practice. 2.1 million people (8% of people aged 45 and over) were diagnosed with having hip osteoarthritis. 16% were women and 11% were men aged 75 years and over. As with non-specific joint osteoarthritis statistics, women were more likely to have sought treatment for hip osteoarthritis than men[58] *Figure 1.12*.

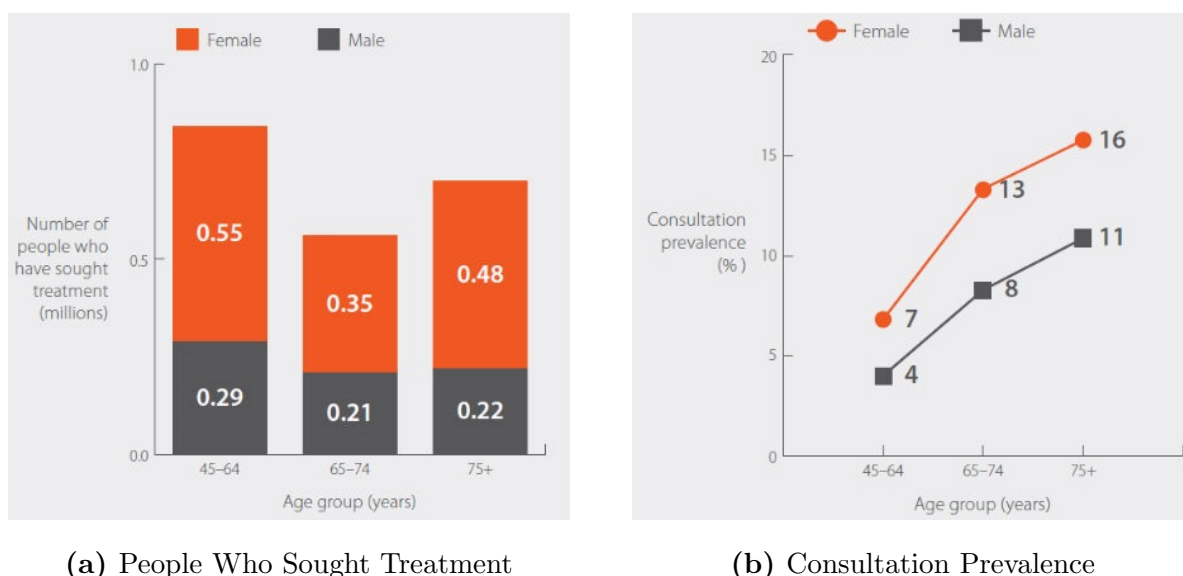


Figure 1.12: Estimated Number Of People In The UK Who Have Sought Treatment, Specifically For Hip OA, By Gender And Age Group
Used From Arthritis Research UK Information Handbook

Hip osteoarthritis is increasing in prevalence in many parts of the world since the disease increases with the age of a population.[60] In Iceland it has been shown that radiographic occurrence of hip osteoarthritis is 5-10% in the general population. The lifetime risk of patients in the United States developing symptomatic hip osteoarthritis is estimated to be 25.3%.[50] Further studies indicate that 5-17% of adults have symptomatic osteoarthritis of the knee and 9% have symptomatic osteoarthritis of the hip.[61]

Numerous population based radiographic prevalence studies for hip osteoarthritis have been performed, see *Table 1.2*[62, 63]. There may be a number of reasons for the apparent variations in osteoarthritis prevalence found in these investigations. Apart from the varying symptoms, clinical examinations and subject history there may be variable radiographic definitions used for hip osteoarthritis and subjective joint space width (JSW) measurements, Kellgren And Lawrence (K&L) scoring depending on the individual radiologist. This makes the comparison of prevalence rates of hip osteoarthritis between different ethnic groups and populations, difficult or perhaps impossible.

First Author	Publication Year	Ethnic Group	Country	Size of population examined	Age	OA definition	Prevalence %		
							Men	Women	Total
Birrell	2005	Caucasian	England	1071	45+	JSW < 1.5mm	-	-	6.4
Croft	1990	Caucasian	England	1315	60-75	JSW ≤ 2.5mm	14.4	-	-
Cvijetic	2000	Caucasian	Croatia	304	45+	K&L ≥ 2	27.1	-	-
Franklin	2010	Caucasian	Iceland	562	60+	JSW ≤ 2.0mm	3.1	8.9	-
Iidaka	2016	Asian	Japan	2975	23-94	K&L ≥ 2	0.3	1.0	-
Ingvarsson	1999	Caucasian	Iceland	1530	35+	JSW ≤ 2.5mm	11.8	10.1	10.8
Ingvarsson	2000	Caucasian	Iceland	1501	35+	K&L ≥ 2	9.9	8.6	9.2
Lawrence	1954	Caucasian	England	501	55-64	K&L ≥ 2	25.0	15.0	19.8
Lawrence	1962	Caucasian	Czechoslovakia	376	55+	K&L ≥ 2	17.0	10.0	13.4
Lawrence	1964	Black	Jamaican	178	55-64	K&L ≥ 2	1.0	-	-
Lawrence	1970	Caucasian	Switzerland	223	55+	K&L ≥ 2	17.0	7.0	11.1
Nevitt	1998	Caucasian	USA	4450	65+	JSW ≤ 1.5mm	-	20.8	-
Nevitt	2002	Asian	China	1506	60+	JSW ≤ 1.5mm	1.1	0.9	1.0
Odding	1998	Caucasian	Netherlands	2895	55+	K&L ≥ 2	14.1	15.9	15.2
Park	2017	Asian	Korea	8976	55+	K&L ≥ 2	0.1	0.2	-
Reijnman	2004	Caucasian	Netherlands	3585	55+	K&L ≥ 2	7.8	6.4	7.0

Table 1.2: Studies On Prevalence Of Hip OA (First Authors, In Alphabetical Order)

1.6.2 Risk Factors Of Hip Osteoarthritis

The pathogenesis of osteoarthritis is multifactorial. Prevalent risk factors for hip osteoarthritis may include age, sex, previous joint injury, obesity, genetic predisposition, and mechanical factors such as abnormal joint shape or malalignment.[64, 65] These risk factors could be grouped into systemic risk factors (age, sex, ethnicity, genetic variables), local risk factors (previous damage, muscle weakness, joint malalignment, increasing bone density) and loading factors (obesity, joint injury, damaging physical activity), see *Figure 1.13*.

Having a multifactorial pathogenesis, osteoarthritis most likely develops from a combination of systemic, local and loading factors. While systemic background factors may predispose a risk of osteoarthritis, it is the local risk factors and mechanical loading factors that may initiate the cascade of joint changes resulting in clinical osteoarthritis. Systemic factors are not generally modifiable but (can, for instance, in extreme genetic phenotypes such as stickler syndrome) give vital clues about the degeneration of joint function from component failure. However, local factors and loading factors generally tend to be modifiable; therefore, potentially intervening in these (diet, muscle strengthening, decrease of damaging physical activity), at the right time, could reduce the risk, or could prolong the health of a hip joint.

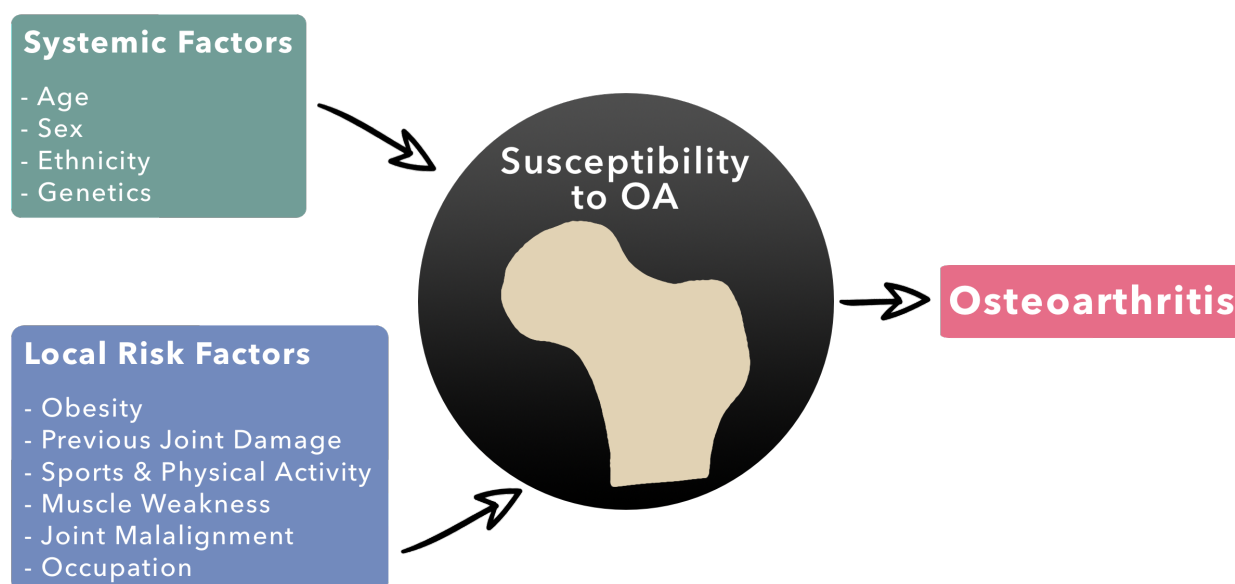


Figure 1.13: Common Susceptibilities To OA

1.6.3 Systemic Risk Factors

Age

It is widely proposed that ageing has a negative effect on the ability to maintain a strong, healthy hip joint. Many believe that the aged hip joint is less able to protect itself from natural bio-mechanical stresses due to degenerative changes in the articular cartilage surface or from acquired joint laxity (which leads to damage from incorrect loading). In a large study of symptomatic osteoarthritis it was observed that the prevalence and incidence of hip osteoarthritis increased sharply with age, particularly after 50, with a decline after age 70.[66] Murphy et al. modelled a 25.3% likelihood of symptomatic hip osteoarthritis development in at least one hip by the age of 85, even after adjusting for ethnicity, body mass index (BMI), sex and previous hip injuries.[50]

Sex

The incidence of hip osteoarthritis increased with age, and women had higher rates than men, especially after age 50 with a subsequent levelling-off or decline in both sexes around the age of 80. As previously mentioned, there is a sharp increase in prevalence of hip osteoarthritis after the age of 45.[61, 54] Prevalence, incidence, and severity of osteoarthritis are different in women than in men. Women are more likely than men to suffer from osteoarthritis.[67–70] A Canadian study determined that women were not only more likely to develop osteoarthritis but had worse symptoms, greater disability and were less likely to have undergone arthroplasty.[71]

The relationship of age and sex is shown in *Figure 1.14*. It shows that men start to slowly lose bone mass at about 50 years of age and women begin to lose it much more rapidly after 50 y/o. This is generally because 50 is the average age at which women go through menopause. Menopause not only lessens and ceases their menstrual periods, but it reduces their ovaries in size. This ceases the production of oestrogen, a hormone that is known to promote osteoblastic activity and production of bone matrix.[72, 73] Promoting nutrition high in calcium and vitamin D and regular weight-bearing exercises early in life (before the age of 30) can maximise bone mass and reduce the risk of bone mass loss.

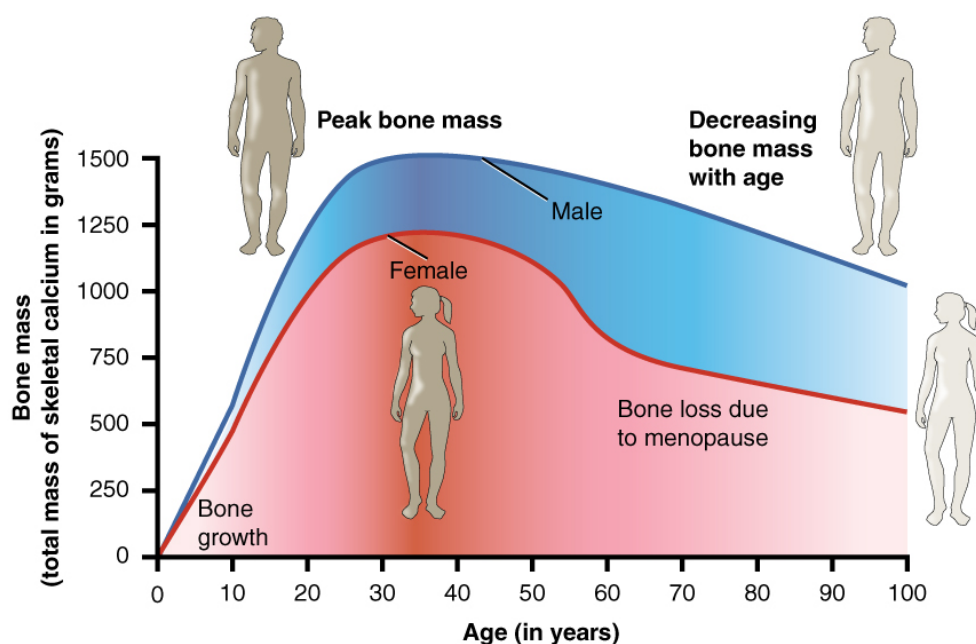


Figure 1.14: Relationship Of Age Vs Bone Mass

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Ethnicity

Ethnicity (where access to orthopaedic surgery joint replacement is equivalent for all groups) appears to influence osteoarthritis development.[74] For instance in a U.S. study of ethnicity,[75] Caucasian subjects had 2-10 times higher THR rates than that of any other ethnic group (African, Hispanic, Asian). Osteoarthritis was the main indicator for THR. Another ethnicity study, carried out in Hawaii,[76] looked at subjects <50y/o and >50y/o. Oishi et al. found a quite low rate of THR for all ethnic groups of Hawaii <50y/o (Caucasian, Japanese, Chinese, Hawaiians, Filipino). Merx et al. studied how total hip replacements rates vary for ethnically Caucasian people in comparison to African, Hispanic and Asian ethnicities in the USA, noting that THR rates varied between 50 and 130 procedures for every 100,000 inhabitants. High annual THR rates were also reported for Scandinavian countries: from 100 to 125 cases per 100,000 inhabitants reported in Norway,[77] Iceland,[62] Sweden[78] and in the Netherlands.[79] When looking at datasets from England,[80] Australia[81] and the west of Scotland,[82] corresponding rates of THR were intermediate, between 65 and 90 per 100,000 inhabitants. In studies conducted between 1988 and 1990, THR rates showed similar findings with between 82 and 105 cases in Denmark,[83] 58 and 105 in Finland,[84] 50 and 105 in Canada[85] and 60 and 105 in Olmsted County (USA).[86] Primary osteoarthritis was the documented indication for >65% THR's performed in these countries.

Genetics

Probably the first mentions of an inheritance factor of osteoarthritis were in papers from the early 1950's where a team investigated families of patients with bony swellings that develop in the joints closest to the end of the fingers and toes known as Heberden's nodes. Stecher et al. found the nodes to be twice as frequent in mothers and three times as frequent in sisters of affected women.[87–89] Since then, numerous studies were conducted on individuals with generalised osteoarthritis and many suggested inheritance to be factor of hip osteoarthritis development. In the late 1980's a study showed that the prevalence of primary hip osteoarthritis in siblings of individuals with primary osteoarthritis was nearly three-fold higher, 8%, compared with 3.8% in controls.[90] The authors of follow up studies concluded that there were strong genetic influences observed in “common hip osteoarthritis” in both women and men.[91, 92] A population-based study looking at twin sisters found a direct relationship between hip osteoarthritis and bone mineral density of the femoral neck of the affected side. The study demonstrated that a higher femoral neck bone density was associated with the presence of osteophytes in the osteophytic affected hip joint. Suggesting that there may be common genes for osteoarthritis and bone formation.

1.6.4 Local Risk Factors

Obesity

The relationship of being obese or overweight and hip osteoarthritis is inconsistent, it is believed that if it does exist, it is a weaker relationship than the one with knee osteoarthritis.[93, 94] Nevertheless there is consistent evidence that increased hip loading from obesity increases the risk of symptomatic hip osteoarthritis.[95] There was “moderate-strong” increased risk of THR with individuals who had a higher BMI.[96–98] A study of 239 men found significant likelihood of hip osteoarthritis development if the BMI was higher than normal.[99] Another study of 134 women also found significant correlations between overweight individuals and symptomatic hip osteoarthritis. A systematic review examined 13 studies of obesity/overweight as a risk factor for (hip and knee) osteoarthritis and overwhelmingly demonstrated an increased risk for hip osteoarthritis with increasing BMI rating (odds ratio (OR) ranged from 1.6 to 15.4).[100] This was consistent with previous such reviews.[97] All studies reviewed by Richmond et al. and Lieveense et al. showed that there was also a greater risk of hip osteoarthritis in obese individuals compared to overweight individuals.

Previous Joint Damage

Numerous studies have shown that there is a greater risk of hip joint osteoarthritis in individuals who have suffered previous injuries to the area.[101, 102] Heliövaara et al. found an association between previous joint damage and hip osteoarthritis after adjusting for age and sex (OR=2.1, 95% confidence interval (CI) 1.4, 3.1).[95] This is particularly the case in those who had suffered fractures or ligament injury. Previous joint damage also includes previous operations that may have been carried out on the femoral head or acetabular socket.

Sports & Physical Activity

Similar to the inconsistent evidence seen in obese individuals, conflicting results have been produced in studies examining the relationship between sports and various physical activities and subsequent osteoarthritis development. Osteoarthritis of the hip joint was found to occur significantly more often in football players than in controls.[103–105] Klunder et al. did not identify football as a risk factor for knee osteoarthritis. Lau et al. identified gymnastics as a risk factor for hip osteoarthritis in women but not in men. Interestingly, running, kung fu and football were not identified as risk factors of osteoarthritis in other studies.[102, 106] Vingaard et al. concluded that medium-high exposure to sports activity before 50 y/o increased the odds of hip osteoarthritis (OR=4.5, 95% CI 2.7, 7.6 and OR=2.6, 95% CI 1.5, 4.5 respectively). They also identified track and field (OR=3.7, 95% CI 1.1, 13.2) and racket sports (OR=3.3, 95% CI 1.2, 12.7) as sports associated with the highest odds of hip osteoarthritis.[104] Lane et al. identified that recreational physical activities performed by women who were highly physically active before menopause may increase the risk of both radiographic and symptomatic hip osteoarthritis.[107] However, another study[108] came to the conclusion that there was no association between regular sporting activity and risk for osteoarthritis. Overall, the mixed results found for any association between sports and hip osteoarthritis were most likely due to the different definitions of “sports related osteoarthritis”. Some studies evaluated a single sport or sport type, while others examined all sports or amount and type of sport. This may have resulted in the heterogeneity of the results. It has been reported that clinical decisions of hip osteoarthritis are often not influenced by radiographic changes but pain and scoring of rotation issues and the limited function of the hip joint.[109, 110]

Muscle Weakness

There is commonly held view among clinicians that there is a relationship between lower extremity muscle weakness and hip osteoarthritis. However, there is far less literature available about this relationship compared to that of knee osteoarthritis. It remains unclear if the same muscles affected and the same muscle weakness seen in knee osteoarthritis is evident in hip osteoarthritis. Loureiro et al. conducted a systematic review to evaluate any potential evidence for muscular weaknesses as underlying mechanisms for hip osteoarthritis.[111] The review included 13 cross-sectional studies evaluating lower extremity muscle strength, size and quality in individuals with hip osteoarthritis. Loureiro et al. found there to be consistent evidence for muscle atrophy and muscle weakness in the leg of the individual that was affected and moderate evidence for smaller muscles of the affected leg in individuals with hip osteoarthritis compared to healthy controls. Eight of the 13 studies reviewed by Loureiro et al. investigated muscle strength between affected and contralateral legs in people with hip osteoarthritis. Predominantly the greatest reduction in muscle strength (in the affected osteoarthritic leg) was seen for the hip and knee flexors and extensors. Studies reported that individuals with hip osteoarthritis have significantly lower abduction, adduction and flexion muscle strength compared to controls.[112, 113] Consistent evidence reported reduced quadriceps muscle size in the osteoarthritic leg compared to the quadriceps muscle size of the contralateral leg. Conversely, a number of studies found no difference in muscle size between the affected leg and a healthy control leg.[114, 115, 112] Grimaldi et al. identified that the gluteus medius, piriformis, and gluteus maximus (see *Figure 1.4*) were smaller in size in individuals with advanced hip osteoarthritis compared to mild-stage hip osteoarthritis; thus, suggesting that muscle volume may be associated with hip osteoarthritis. Two studies that looked at muscle quality in hip osteoarthritis reported lower radiological muscle density in the osteoarthritic leg.[113, 116]

Joint Malalignment

Joint alignment is very important for correct load distribution. Any changes from the neutral alignment of the hip will undoubtedly affect the load distribution and forces applied on the femoral head. The angle alignment of the femoral head is important for the movement of an individual, see *Figure 1.15*. The normal inclination angle of the femoral head is said to be between 120-130 degrees (coxa norma).[117] In the elderly it is generally

closer to 130 degrees, and any increase beyond this results in coxa valga. However, if there is a decrease below 120 degrees, it results in coxa vara. The angle of torsion is also an important alignment; for individuals termed “normal” the angle is ranged between 12-20 degrees. If the angle is beyond 20 degrees, it is termed as anteversion; if the angle is below 12, degrees it is termed as retroversion.

Coxa profunda refers to a deep acetabular socket. On pelvic X-rays it is seen as the acetabular fossa being medial to the ilioischial line. It should be differentiated from protrusio acetabuli, where the femoral head is seen additionally medial to the ilioischial line. Coxa profunda is much more common in females.

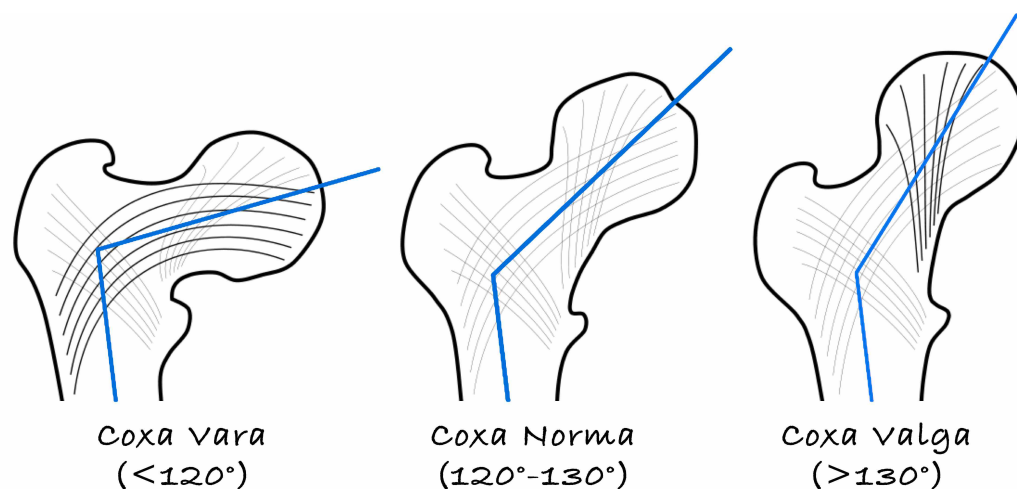


Figure 1.15: Deformities Of The Hip Angle

Adapted From <https://commons.wikimedia.org/wiki/File:Coxa-valga-norma-vara-000.png>,
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In general, most structural changes may lead to malalignment of the hip joint which in turn may lead to hip osteoarthritis. Some of which may include pistol-grip deformity,[118, 119] tilt deformity,[120] and femoral anteversion.[121] Acetabular deformities, may include coxa profunda, protrusio acetabuli[122] or retroversion.[123, 124]

Tönnis et al. reviewed studies carried out investigating the measurements of torsion.[121] The team found 4 studies[125–128] that supported a hypothesis of anterversion creating a predisposition of hip osteoarthritis, and 3 studies[129–131] that showed that it does not. Following the review study, Tönnis et al. suggested that reduced femoral and acetabular anteversion may result in hip osteoarthritis. Jacobsen et al. found that the presence of hip dysplasia (a decrease in the center-edge angle) significantly influenced the likelihood of hip osteoarthritis.[132] Similar studies found a strong association between acetabular dysplasia and incident radiographic hip osteoarthritis.[133, 134]

Occupation

Richmond et al. reviewed 9 studies investigating occupation as a potential risk factor for hip osteoarthritis.[100] All 9 studies reported a significantly greater risk of developing hip osteoarthritis in individuals with occupations involving physically demanding activities such as heavy lifting, kneeling, climbing stairs and other highly physical demands. Lau et al. found that climbing stairs increased the risk of osteoarthritis (OR=12.5, 95% CI 1.5, 104.3) in men and heavy lifting increased the risk of osteoarthritis in women (OR=2.4, 95% CI 1.1, 5.3).[102] In a similar study investigating prolonged and frequent heavy occupational lifting as a cause of hip osteoarthritis, Cogon et al. found no comparable association among women but an association in men (men who regularly lifted weights of >50kg for +10 years had an OR=3.2, 95% CI, 1.6, 6.5).[135] Studies have found that due to the work that farmers do on a day to day basis, they have a high prevalence of hip osteoarthritis.[136] The cross-sectional survey of Heliövaara et al. in individuals exposed to 3 or more physical occupational stresses (lifting, stooping or the use of a vibrating tool) found the adjusted odds ratio to be OR=2.4(95% CI 1.4, 3.8) for unilateral hip osteoarthritis and OR=2.8(95% CI 1.6, 4.7) for bilateral hip osteoarthritis.[95] The results that Richmond et al. identified were consistent with previous reviews that investigated how occupational activities negatively affected the hip and increased the likelihood of hip osteoarthritis development.[137, 138]

Both systemic and local risk factors contribute in part to the development of hip osteoarthritis. The biomechanics of highly focal concentrations of load within parts of the hip joint and have an effect on contact areas such as the labrum and cartilage. When 2-4 times the body weight is transferred through the proximal femur, the abnormal increase in body mass has a predictable effect on hip joint wear. Some diseases of the hip (perthes disease, developmental dysplasia) may lead to premature wear. Femoroacetabular impingement (FAI) is likely caused by bone/joint adaptation to high specific loading patterns, for example, certain sports (football) during adolescence/skeletal growth. Intense sports or occupational factors may increase the likelihood of hip damage in a number of different ways; there may be acetabular tears, stress damage of subchondral bone or cartilage contusions.

1.6.5 Symptoms, Signs And Diagnosis Of Hip Osteoarthritis

The principal symptom of clinically relevant hip osteoarthritis is pain.[108] This is typically felt deep in the groin but may be felt over a wide area including the lateral thigh and buttock, anterior thigh and even knee. Pain is initially felt on walking, but in advanced cases often even occurs at rest and at night. Stiffness is common in patients and they may have difficulty doing routine tasks, such as bending over to put on socks and shoes. An assessment of the walking profile, as well as passive and active moment of the hip joint, is necessary. During clinical examination (particularly during bending, adduction, internal rotation and maximal flexion) painful restrictions of both active and passive movements of the hip are seen. Clinical diagnosis of hip osteoarthritis is usually based on a combination of patient history and clinical examination, whereas staging/grading can be achieved through radiography of the hip.

1.6.6 Pain Scores For Osteoarthritis Assessment

The establishment and evaluation of existing osteoarthritis related pain measures is key to any pain score assessment. It is therefore important that all recommendations regarding the measurement of pain, physical function, and joint structure of individuals with hip osteoarthritis are conducted to a high standard using a recognised method. This makes it essential to have a purpose-built multidimensional instrument with an ability to measure clinically vital, patient-relevant symptoms in Osteoarthritis of the hip. Pain scores are an important part of assessing whether osteopaths among other healthcare professionals are improving the symptoms reported by their patients. The Oxford Hip Score (OHS) and the Western Ontario and McMaster Universities (WOMAC) are examples of Patient Reported Outcome Measure (PROM) assessing pain scores.

A PROM is as “a report coming directly from patients about how they feel or function in relation to a health condition and its therapy without interpretation by healthcare professionals or anyone else”[139]. It directly establishes if treatment has improved a patient’s symptoms, health and well-being, if patients are satisfied with their treatment as well as the type of experience of care that patients received.

The OHS is a short report usually asking patients 12 questions about activities of daily living, specifically designed to assess feedback on function and pain with patients undergoing hip replacement surgery. It is reproducible and sensitive to clinically important patient changes.

The WOMAC is a self-administered questionnaire consisting of 24 questions divided into 3 sections. Pain (5 questions), Stiffness (2 questions) and Physical function (17 Questions)

1.6.7 Investigation

Management algorithms are in widespread usage in primary care. The following have been summarised for a clearer understanding.

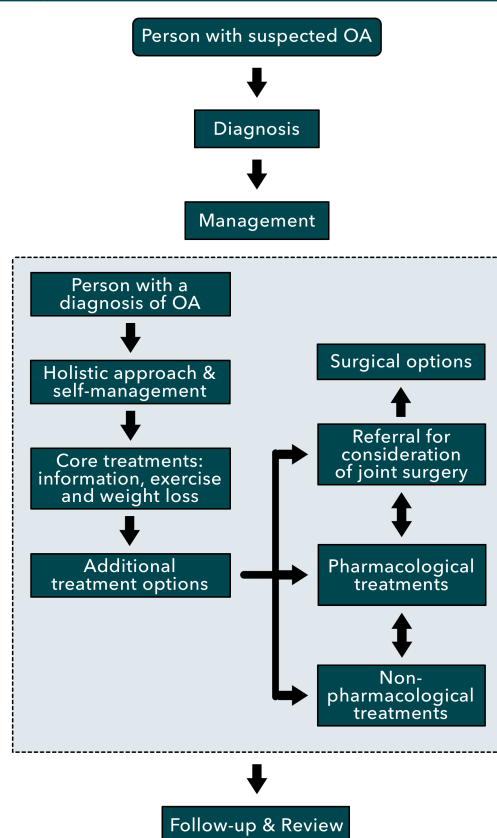
These include:

- (a) National Institute for Health and Clinical Effectiveness (NICE) CG177 and QS87
- (b) Arthritis Alliance of Canada (AAC) and the Centre For Effective Practice Guidance Tool (CFPC)
- (c) Royal College of Surgeons Guideline (RCS)
- (d) European League Against Rheumatism Guideline (EULAR)

NICE CG177 and QS87

The Osteoarthritis Care And Management Clinical Guideline (2014) and the Osteoarthritis Quality Standards (2015) mention that the results of X-rays and scans do not explain symptoms or help when deciding about treatment. Avoiding imaging in osteoarthritis reduces both potential harm from exposure to radiation from X-rays and costs of unnecessary imaging.

NICE Osteoarthritis Care & Management Clinical Guideline* [CG177]



*Osteoarthritis Care and Management Clinical Guideline (2014)

(a) NICE Clinical Guideline 177

NICE Quality Standard* [QS87]

The quality standard for osteoarthritis is made up of 8 statements that describe high-quality care for adults with osteoarthritis.

1. Adults aged 45 years or over who go to their GP with joint pain that is typical of osteoarthritis are usually diagnosed with osteoarthritis without the need for an X-ray or a scan. This is because the results of X-rays and scans do not explain symptoms or help when deciding about treatment, and will mean that people do not have unnecessary X-rays or scans.
2. Adults who have been diagnosed with osteoarthritis have an assessment in which they are asked about their pain, how they are managing on a day-to-day basis and how the condition is affecting their life overall, including their mood. This will help when deciding the best way to try to improve their symptoms and quality of life.
3. Adults with osteoarthritis agree a self-management plan with their GP or nurse that covers what they can do to help manage their condition, including improving their symptoms and quality of life. The plan should identify where they can get the support they may need to help them do this.
4. Adults with osteoarthritis are advised and encouraged by healthcare professionals to exercise, both for general fitness and to strengthen the muscles that support their affected joints, because this may help to improve their symptoms.
5. Adults with osteoarthritis who are overweight or obese are offered help to lose weight, because being overweight can make joint pain worse and losing weight should improve symptoms.
6. Adults with osteoarthritis discuss and agree (usually with their GP or practice nurse) when they should have their next review to check how well they are managing and if they need any more support. The timing of their next review will depend on how much their osteoarthritis is affecting them and how well any treatment is working.
7. Adults with osteoarthritis are given information, and are advised and supported to exercise and (if appropriate) lose weight to help with joint pain and stiffness, for at least 3 months before any referral for possible joint surgery.
8. Adults with osteoarthritis who are considering joint surgery discuss this with their healthcare professional to decide if it is right for them, and are not denied a referral because they have not met particular requirements.

*Osteoarthritis Quality Standards (2015)

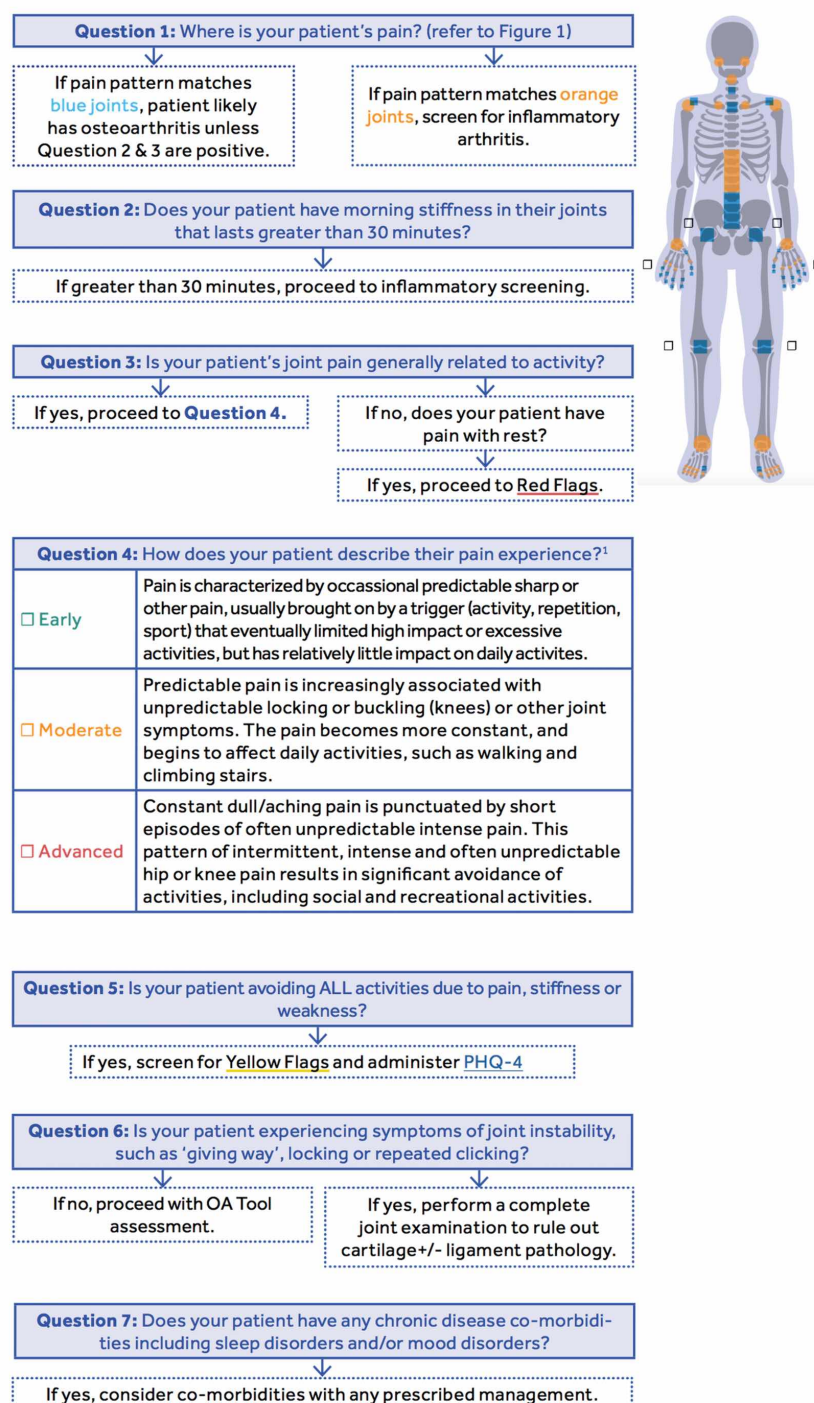
(b) NICE Quality Standards 87

Figure 1.16: NICE Guidelines And Quality Standards

AAC/CFPC

The Osteoarthritis Tool (2017) mentions that radiography does not reliably correlate with symptoms, so suggest to reserve X-rays only for patients with advanced hip disease by clinical examination.

CFPC Arthritis Alliance of Canada/Centre For Effective Practice Guidance*



*Centre for Effective Practice Guidance Osteoarthritis Tool (2017)

Figure 1.17: CFPC Osteoarthritis Tool

Image Taken From Document

RCS

The Pain Arising From The Hip In Adults (2017) mention that a record needs to be kept of: history taking examination, and the if deemed necessary, plain anteroposterior (AP) radiograph. Referral to secondary care particularly when hips are painful and stiff, interfering with activities of daily living, work or leisure and not responsive to conservative measures, in which case a narrowed hip joint space is one of 4 clear indications for joint replacement surgery.

RCS Royal College of Surgeons Guideline*

History - pain in the groin, medial thigh and greater trochanter radiating to thigh and knee at rest and/or after activity or isolated knee pain condition having an impact on occupation, daily activity and sports (e.g. decrease in walking distance, disability in negotiating stairs and performing pedicure).

Examination - examine the hip for tenderness and irritability on movement.

Investigations - a plain A-P radiograph of the pelvis may be requested to confirm the diagnosis after history and examination.

No further imaging (e.g. MRI or bone scan) is appropriate before referral.

*Pain arising from the Hip in Adults (2017)

Figure 1.18: RCS Osteoarthritis Guidelines

EULAR

The Recommendations For The Use Of Imaging In The Clinical Management Of Peripheral Joint Osteoarthritis (2016) mention that imaging is not required [...] in patients with typical presentation of osteoarthritis.

EULAR Recommendations for OA management

Recommendation	Level of Evidence
1. Imaging is not required to make the diagnosis in patients with "typical" presentation of OA.	III-IV
2. In atypical presentations, imaging is recommended to help confirm the diagnosis of OA and/or make alternative or additional diagnoses.	IV
3. Routine imaging in OA follow-up is not recommended. However, imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics to determine if this relates to OA severity or an additional diagnosis.	III-IV
4. If imaging is needed, conventional (plain) radiography should be used before other modalities. To make additional diagnoses, soft tissues are best imaged by US or MRI and bone by CT or MRI.	III-IV
5. Consideration of radiographic views is important for optimising detection of OA features; in particular for the knee, weightbearing and patellofemoral views are recommended.	III
6. According to current evidence, imaging features do not predict non-surgical treatment response and imaging cannot be recommended for this purpose.	II-III
7. The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner and imaging may improve accuracy. Imaging is particularly recommended for joints that are difficult to access due to factors including site (eg, hip), degree of deformity and obesity.	III-IV

*EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis (2016)

Figure 1.19: EULAR Osteoarthritis Recommendations

1.6.8 Treatment of OA

At present, there is no cure for osteoarthritis, it can only be managed with evidence-based symptomatic management, divided into surgical, pharmacological and non-pharmacological treatments. None of these treatments are perfect. Surgical intervention[140] as well as direct articular cartilage repair[141] lead to improvements; whilst pharmacological treatments are usually used for pain relief rather than prevention or cure. Aside from some experimental drugs (such as strontium ranelate, now withdrawn due to safety concerns)[142] they have not been shown to alter the progression of osteoarthritis.[143] Therefore, the need for biomarkers that can predict osteoarthritis onset, monitor progression and evaluate response to therapy is growing.[144] For any form of osteoarthritis, clinicians are reluctant to undertake invasive surgical procedures such as THR. Clinicians aim to educate patients about the disease and how to manage it. If the recommended lifestyle changes (weight loss and exercise,[145] orthotics[146, 147] and pain medications[148]), do not alleviate the symptoms of osteoarthritis, further (more invasive) treatments are suggested by a clinician.

1.6.9 Non-Steroidal Anti-Inflammatory Drugs

A pharmacological approach is always where clinicians start when dealing with osteoarthritis complaints. However, it is always a challenge to decide which medications will provide a particular patient with the greatest symptom relief and cause the least harm. Analgesics such as Paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been commonly used as pharmacological treatment.[149] In 2006 a comparative effectiveness review by Chou et al. was published about analgesics use for osteoarthritis by the Agency for Healthcare Research and Quality (AHRQ). Paracetamol (up to 4g/day) is an oral analgesic chosen for mild to moderate pain in osteoarthritis.[150] NSAIDs decrease pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. They work by blocking different COX isoenzymes (in particular COX1 and COX2). COX1 mediates the mucosal protection of the gastrointestinal (GI) mucosa, protecting the area from acid and platelet aggregation. COX2 mediates effects on pain and inflammation in joints and muscles. By blocking COX2, NSAIDs have been shown to reduce pain compared to placebo in patients with arthritis[151] and lower back pain.[59] However, non-selective NSAIDs have also been noted to block COX1 enzymes causing GI bleeding.[152] The number of deaths in the United States estimated that there were 3200 deaths annually in the 1990s due to the use of non-aspirin NSAIDs.[153]

Topical NSAID are pain and inflammation relieving gels, creams, patches or sprays that are applied directly to painful areas of the body. They work differently from painkillers that are taken orally and dissolve (releasing their ingredients) into the bloodstream. Oral NSAIDs have been associated with potential gastrointestinal (GI), renal and cardiovascular toxicity.[154, 155] Topical NSAIDs have been shown to be beneficial in reducing the likelihood of an individual experiencing adverse effects commonly associated with systemic therapy. Studies have indicated that topical NSAIDs can achieve therapeutic concentration of drug in localised tissues without raising serum levels, and thus potentially avoiding systemic toxicity.[156, 157]

Other topical NSAID advantages[156, 158] include:

- Avoid first pass metabolism and GI tract variability common with drug delivery.
- Administered directly and immediately to local area of pain.
- Topical application may be more acceptable to patients, may increase adherence.
- Avoid drug-drug interactions or adverse reactions.
- Potentially decreased time to efficacy due to elimination of dosage titration.

Most disadvantages of topical NSAID applications are to do with local skin irritation,[159] or the effectiveness of drug molecules penetrating the skin (must be $<500\text{Da}$ in order to diffuse across the stratum corneum and penetrate to the painful site).[160]

1.6.10 Hip Injections

Injections into a joint are a very simple (but invasive) method to relieve pain in a joint; a mild local anaesthetic and steroid mixture is prepared and injected into the area of pain.[161] This is a short-term pain relief as the effects of the local anaesthetic eventually dissipate; the effect of the steroid, however, is longer lasting. The anaesthetic is responsible for pain relief, while the steroid is responsible for the commonly occurring inflammation associated with arthritis.

A technique known as viscosupplementation has been developed, it uses hyaluronic acid (HA), which is a molecule with rheostatic properties.[162] The aim of this treatment is to lubricate the joint to relieve pain.[163] A study has shown modest improvements for os-

osteoarthritis patients, and profound improvements in patients <65 years with less severe osteoarthritis development.[164] Experimental approaches include tanezumab (anti-nerve growth factor therapy) and various modifies of the voltage-gated sodium channel (NAV) 1.9 pathway-hormone doubt is last on the safety of complete pain relief in osteoarthritis.

Nevertheless, a study has suggested that pharmaceutical pain relief for osteoarthritis is not safe for long term use.[165] The effects of pain relief injections may accelerate degenerative changes as patients may not be able to realise when their joint is being overloaded. Pain receptors are present naturally to prevent further damage of joints.[166]

1.6.11 Hip Arthroscopy

Hip arthroscopy or keyhole surgery as it is sometimes known is used to both diagnose and treat problems with joints. It is usually a reasonable treatment for patients with movement constrictions and undefined pain in the groin area. There are more than 1 million arthroscopy operations annually worldwide.[167] The principle is to insert a probe (4.5mm in diameter) into a joint under anaesthetic. A camera and computer attached to the probe allows the clinician to directly observe the cartilage and bones of the joint in real-time. An accurate assessment of the disease can be made, any loose bones can be removed, joint surfaces can be cleaned, cartilage and ligaments could be trimmed (collected and removed) using the attached surgical instruments.[168] This method is not necessarily an osteoarthritis cure; its purpose is to relieve the pain and discomfort in a joint. Therefore, it is a procedure which is most useful for younger patients and/or athletes[169] who are still physically very active. This procedure will prolong their active lifestyle because a joint replacement would prevent them from many physically demanding activities.

1.6.12 Femoacetabular Impingement

In the hip joint, arthroscopy is a procedure used to treat a condition known as FAI.[170] Arthroscopy offers a minimally invasive and effective treatment for FAI. FAI occurs when the AP aspect of the femur catches on the anterior aspect of the hip socket. FAI symptoms include stiffness and pain in the groin, thigh and/or hip, (both at rest and during activity) as well as an inability to flex the hip beyond a right angle. It is a condition in which excess bone grows on the femur or acetabulum. This bone overgrowth or “bone spurs” usually grow into irregular shapes, and because they no longer fit together perfectly, they cause abnormal

contact, and begin to rub against each other. This can result in tears of the labrum. With FAI, pain and rotational limitations develop over time as the joint gets damaged.

Short-term outcomes of FAI were uniformly successful in previous studies.[171] However, it is difficult to say that hip arthroscopy provides documented, reliable and prolonged relief for FAI. When searching for long-term outcomes, hip arthroscopy has demonstrated statistically significant patient-related outcome improvements at minimum 5-year follow-ups.[172] However, currently there is insufficient literature to support hip arthroscopy being superior to open surgical techniques.

There are three recognised types of FAI: cam, pincer, and a combination of both cam and pincer, see *Figure 1.20*.

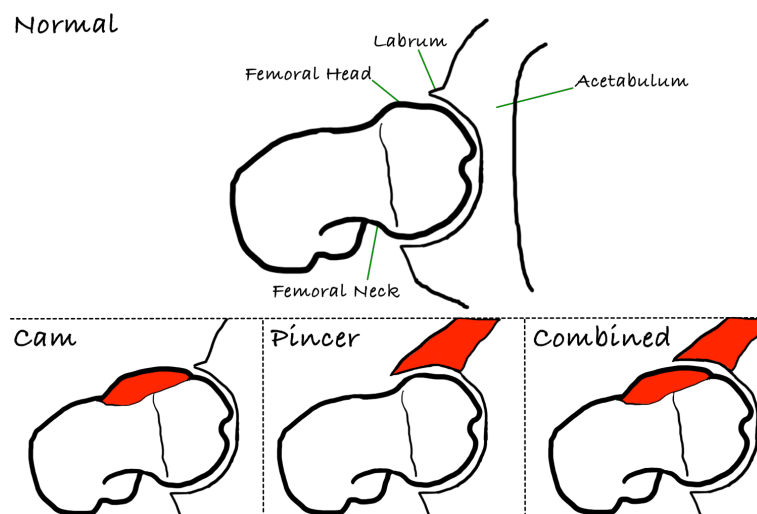


Figure 1.20: Different Types Of Femoroacetabular Impingement

In Cam impingement the femoral head is no longer completely round; therefore it can no longer rotate smoothly inside the acetabulum. Bone spurs on the edge of the femoral head begins to grind with the cartilage inside the acetabulum. In Pincer impingement, the femoral head is excessively covered by the acetabulum. This impingement interferes with the rim of the joint socket and may result in both cartilage and labral tearing. In combined impingement, both cam and pincer type of changes are present at the same time.

Arthroscopy is used to treat FAI by reshaping the damaged area and removing excess bone in Cam or Pincer type of FAI. The operation is carried out (under general anaesthesia) by inserting an optical device (arthroscope) and a drilling instrument (burr) into the joint through small incisions in the skin, see *Figure 1.21*. The leg is rotated and the femoral head

is drawn 1-2cm[173] out of the socket onto an extension table so that both assessment and treatment (smoothing out and reshaping excess bone growth) of the joint can begin.

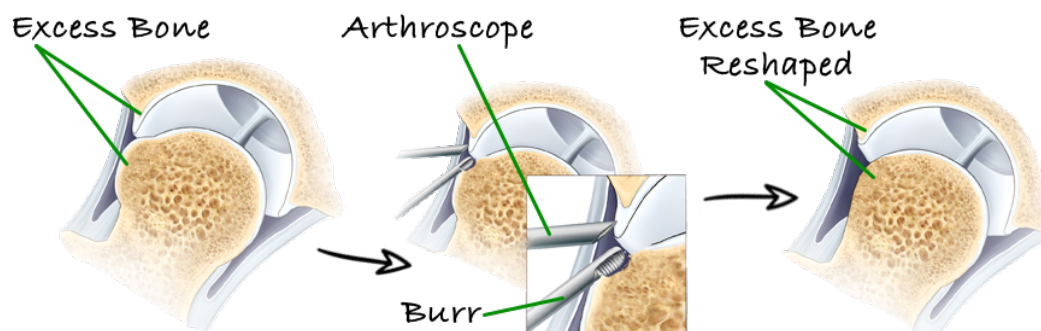


Figure 1.21: Repairing FAI Using Hip Arthroscopy

Image Adapted From <https://www.fairview.org/patient-education/40139> On 10th December 2017

FAI may lead to other problems, such as labral tears. The labrum is a strong, flexible ring of cartilage attached to the inner part of the hip socket. When the labrum is torn, symptoms included: pain, clicking or locking in the joint. If a labral tear has been identified during arthroscopic surgery, it can also be treated by removing, cutting, shaving or heating the tissue.[173] An anchor is implanted into the acetabulum and a suture ties the repaired labrum to the anchor so that it can heal, see *Figure 1.22*.

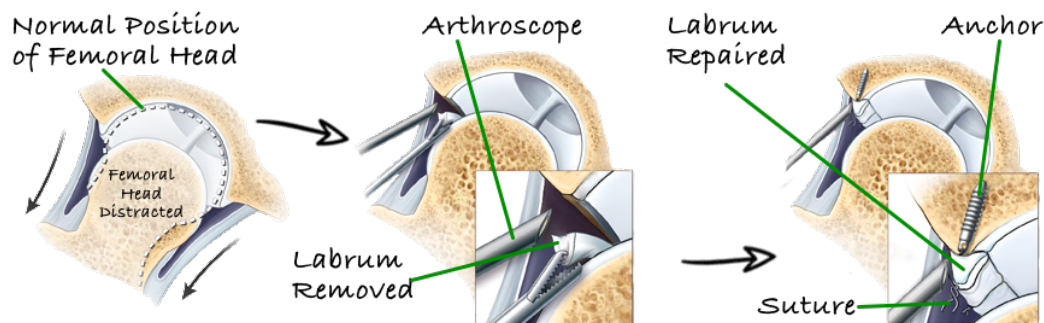


Figure 1.22: Repairing Labral Tears Using Hip Arthroscopy

Image Adapted From <https://www.fairview.org/patient-education/40135> On 10th December 2017

The removal of bone spurs improves joint mobility, increases the area of joint rotation and removes painful constrictions. Correcting FAI can help prevent further damage, however, not all of the damage can be entirely fixed using arthroscopic surgery, especially if the damage has not been detected early and is severe. It is currently the best way to treat painful FAI. Irrespective of which FAI type is being treated, there may be complications with both. Cam lesion resection can prove to be difficult if the bone spur extends posteriorly, this may result in both over and/or under-resection. Pincer abnormalities are difficult to treat because acetabular trimming usually requires labral detachment and re-attachment, and this is a very precise and technically demanding procedure.

1.6.13 Hip Cell-Based Therapy

Cell-based therapy for cartilage repair has been developing rapidly. It has the potential to offer a solution to the repair and regeneration of cartilage and alleviate the pain and symptoms associated with osteoarthritis. The most common types of cell therapy treatments are the use of chondrocytes and mesenchymal stem cells.

Autologous chondrocyte implantation/transplantation (ACI/ACT) first described by Brittberg et al.[174] has been used in clinical practice with >15,000 patients already receiving this treatment around the world.[175] ACI techniques have also shown successful outcomes in the hip.[176] The ACI process consists of three steps. First, a sample (~200mg) of hip cartilage tissue is collected (arthroscopic biopsy) from a healthy region of the joint. Then, enzymes are used to remove the extracellular matrix and isolate the chondrocytes in order to be cultured in vitro. Finally, when enough cells have been acquired, they are implanted into the damaged zone of articular cartilage in another arthroscopy procedure. Since Brittberg et al. first performed ACIs, there have been tremendous advances in the refinement of the technique, with the most recent ACI procedures ensuring long-term cell maintenance and reduced surgical times.[177] Clinical outcomes of long-term follow-ups were reported with ~90% achieving good to excellent results.[178, 179] On the 4th October 2017, NICE made a recommendation for ACI for treating symptomatic articular cartilage defects of the knee. This allowed therapy to be administered within the National Health Service (NHS) (the result of many years of pioneering work led by Professor James Richardson). Separately a commercial product Carticel was initially approved by the Food And Drug Administration (FDA),[180] however, it was suggested to not be used for general osteoarthritis treatment[181] because ACI is only applicable to local cartilage defects surrounded by healthy cartilage. Osteoarthritis on the other hand often affects large areas of cartilage disturbing the homeostasis of an entire joint (not a small local defect). If chondrocytes are implanted in this environment, they may undermine the efficacy of the repair process and cause undesirable differentiation or general apoptosis.[182, 183] In 2016 the FDA approved Maci (based on Carticel) as the first product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee.[184]

Significant clinical safety issues have not been reported using the ACI technique, however, some of its requirements occasionally make it difficult to fulfil: there may be limited cell numbers available, at least two surgical procedures are necessary, in vitro chondrocyte growth

takes time, and the donor-site must be damaged when initially harvesting cells.[185, 186] Mesenchymal stem cells (MSCs) have been suggested as a potential cell source to use instead of a harvested cartilage biopsy. MSCs can be easily collected from numerous tissues around the body such as bone marrow, adipose tissue and the synovial membrane. MSCs grow and divide at a fast rate and are known to have immunosuppressive activities.[187–189] In several clinical trials, bone marrow-derived MSCs have shown encouraging signs in the treatment of knee osteoarthritis, significantly improving cartilage quality and decreasing pain but this has not been investigated on large data sets.[190, 191]

1.6.14 Hip Osteotomy

Osteotomy, also commonly known as bone realignment, is a procedure that requires cutting through a bone to create a surgical fracture to realign a hip/knee, and thus altering the stresses of walking with the potential of pain relief,[192, 193], see *Figure 1.23*. Osteotomy is highly invasive and is generally more successful for patients, who have an extensive range of motion of the diseased joint before the operation. The procedure may delay the need for total joint replacement for 5-10 years.[194] This is again a procedure which does not cure osteoarthritis but delays the need for a THR.

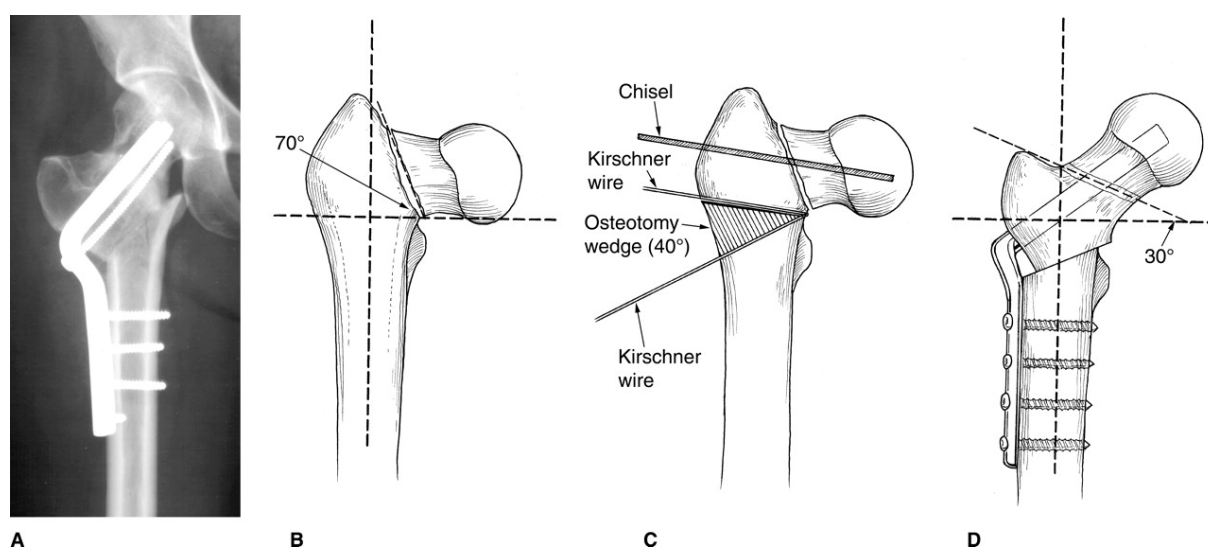


Figure 1.23: Hip Osteotomy Procedure

Image Used From[195]

1.6.15 Total Hip Replacement

When the pain of osteoarthritis becomes too unbearable and neither medications nor previously mentioned invasive treatments have helped the patients, the clinician uses clinical assessment and imaging techniques to confirm suitability for joint replacement. This decision is usually made when X-rays confirm joint space narrowing (JSN) reflecting severe cartilage wear or severe JSN.[196] However, it should be noted that the correlation between X-ray findings of osteoarthritis features and symptoms is poor, and often the clinical assessment of an experienced surgeon is the key to patient selection. In a total hip replacement procedure, the damaged bone of the femoral head and its cartilage is removed and replaced with prosthetic components. The typical replacement components used for the prosthetics, see *Figure 1.24*.

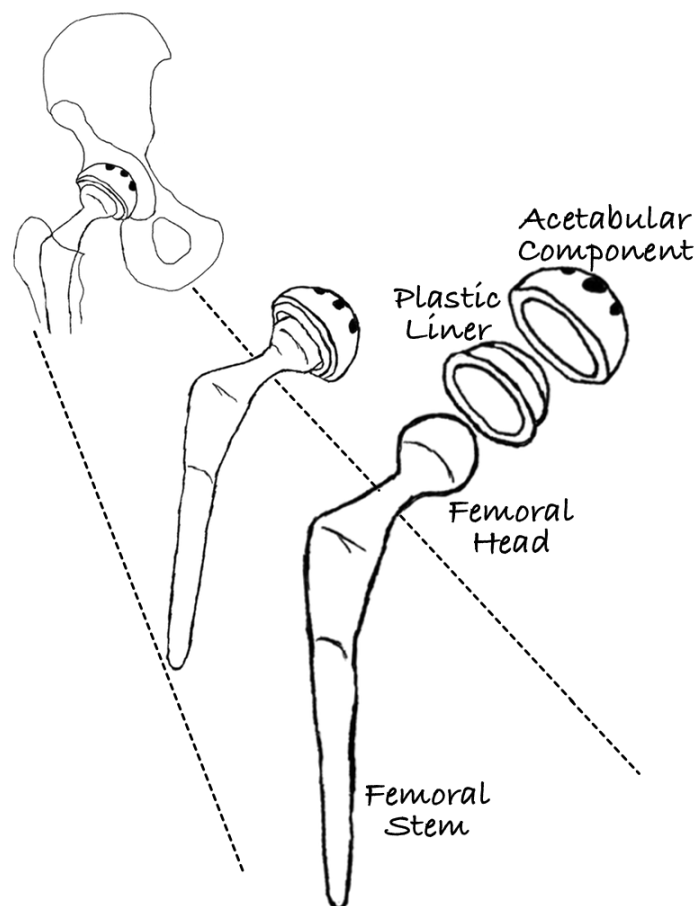


Figure 1.24: Individual Components Of A Total Hip Replacement, Merged Into An Implant And Then Fitted Into A Hip

First the damaged femoral head is surgically removed, the femur is hollowed out in the centre and a metallic femoral stem may be either cemented or “press fitted” into the hollow bone.

A metallic or ceramic ball is attached to the upper section of the femoral stem in order to replace the femoral head that was surgically removed. The damaged cartilage surface of the acetabulum is ground down with specialised tools and is replaced with a metal socket. Screws or cement hold the socket to the hipbone. A tough plastic or ceramic spacer is enclosed between the new ball and the socket arrangement allowing for a smooth gliding surface and rotation to mimic motion angles of the original femoral head.[197] The materials used have evolved over time and differ depending on country, hospital and surgeon preference and/or availability. There are advantages and disadvantages to the different components available on the market.

Generally, THR is extremely effective for symptom improvement and function restoration. Feedback from a national survey conducted, known as Patient Reported Outcome Measures (PROMs) for patient satisfaction “before and after a THR replacement” (taken from 93,881 hip replacement patients who filled in questionnaires between 2009 and 2012) reported that 85.6% of patients felt much better and could be more active postoperatively (in later years such as 2015, 2016 and 2017 numbers higher than 90% were reported, and thus patient satisfaction post THR replacement appears to be constantly increasing).

Following extensive research and patient studies, Arthritis Research UK claim that approximately 80% of cemented hips last for 20 years.[198] *Table 1.3* summarises the number of hip replacements in England and Wales in 2011, it also includes revision surgeries. Of the 80,314 surgeries carried out in 2011 for THR, 11% were revision replacement surgeries.

Type of Joint Replacement	Number	Equivalent
Initial replacement	71,672	89
Revision replacement	18,641	11
Total	80,314	100

Table 1.3: Number Of THR Replacements In England And Wales In 2011

According to the latest annual report published by the National Joint Registry (NJR) the total number of primary hip replacements (majority due to osteoarthritis) performed continues to increase with 87,733 performed in 2016, compared to 86,496 in 2015.[199]

A comprehensive summary of treatment strategies that have shown potential disease modifying properties is included in *Appendix A*.

Chapter 2

Imaging Modalities In Assessment Of Symptomatic Osteoarthritis

2.1 Background

Historically, a typical clinical assessment pathway for adults presenting with hip osteoarthritis would have resembled the box below.

1. Persistent hip or groin pain

Particularly night pain

Functional limitation (reduced mobility, antalgia)

2. Primary care assessment

Clinical assessment of joint

Pain, range of joint motion (ROM)

Plain X-ray of the hips

3. Primary care non-surgical management

Analgesia

Aids (walking stick)

Physiotherapy and lifestyle/exercise advice

4. Secondary care musculoskeletal/orthopaedic assessment

For persisting symptoms and limitation despite therapy

[Plain X-ray of the hips to grade progression*]

5. Surgical decision making between orthopaedic team and patient

Selecting appropriate patients for total hip replacement (THR)

*denotes the steps now removed by current expert consensus guidelines[200]

Hip osteoarthritis is a progressively degenerative disease of the joint and a leading cause of pain and disability in older adults. Prevalent risk factors for hip OA include age, sex, previous joint injury, obesity, genetic predisposition, and mechanical factors such as abnormal joint shape or alignment.[64, 65] There has been a 20% increase in cases of OA since 2002.[42] Estimates from the US suggest that hip replacements for OA will increase 174% by 2030.[43] A typical clinical assessment pathway for adults presenting with hip OA (for instance, the 2017 Royal College of Surgeons (RCS) “Pain Arising From The Hip In Adults” guide) advocates history of examinations taken and, if deemed necessary, plain AP radiograph and referral onwards to secondary care, particularly when hips are painful and stiff; interfering with activities of daily living, work or leisure and not responsive to conservative measures. Indeed, the RCS guide highlights a narrowed hip joint space as one of 4 clear indications for joint replacement surgery. However, four recent guidelines (including one specifically on OA imaging[200]) now recommend that medical practitioners avoid the use of imaging in all forms of OA, basing the recommendations mainly on research showing that hip pain and imaging findings are quite discordant.[201] Some recommendations are constructive, e.g. a North American Osteoarthritis patient management tool which states that; “Radiography does not reliably correlate with symptoms” (but does advocate X-ray only for patients with advanced hip disease by clinical examination). Some limit the extent of their recommendation to “diagnosis”, such as the EULAR Osteoarthritis imaging guideline stating, “Imaging is not required to make the diagnosis in patients with typical presentation of OA”. Others, such as NICE (UK) Clinical guidelines and Quality, are hostile towards imaging of all forms in osteoarthritis, referencing “[...] potential harm from exposure to radiation from X rays and costs of unnecessary imaging [...]” and “the results of X rays and scans do not explain symptoms or help when deciding about treatment.” Others, such as NICE (UK), highlight harms and encourage imaging avoidance, see *Table 2.1*.

Many clinicians feel that X-rays and scans do help when deciding about treatment. Given the very high success and satisfaction rate following THR, but the very high cost of this definitive procedure (\$13.4 billion in 2004 for all joint replacements in the US[202]), tools are needed that can stratify patients with hip pain within a typical patient pathway. If a cost-effective imaging investigation could reassure patients and their clinicians that THR is unlikely to be needed in the medium term, it would allow them to concentrate on effective lifestyle modification and self-management. By focusing on the poor correlation between

imaging findings and pain, guideline writers may have missed where the utility of imaging in osteoarthritis resides, in helping stratify patients who might benefit from referral to orthopaedic surgical services and reassuring those who are unlikely to require it in the near future.

Guideline	Recommendation
<i>Pain arising from the Hip in Adults (2017)</i> Royal College of Surgeons Guideline (RCS)	History taking, examination, and then, if deemed necessary, plain AP radiograph. Referral to secondary care, particularly when hips are painful and stiff, interfering with activities of daily living, work or leisure and not responsive to conservative measures, in which case a narrowed hip joint space is one of four clear indications for joint replacement surgery.
<i>Osteoarthritis care and management Clinical Guideline(2014) and Osteoarthritis Quality Standards (2015)</i> National Institute for Health and Clinical Effectiveness (NICE CG17 and QS87)	The results of X-rays and scans do not explain symptoms or help when deciding about treatment. Avoiding imaging in osteoarthritis reduces both potential harm from exposure to radiation from X-rays and costs of unnecessary imaging.
<i>Osteoarthritis Tool (2017)</i> Arthritis Alliance of Canada/Centre for Effective Practice Guidance Tool (AAC/CEP)	Radiography does not reliably correlate with symptoms, so reserve X-ray only for patients with advanced hip disease by clinical examination.
<i>Recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis (2016)</i> European League Against Rheumatism Guideline (EULAR)	Imaging is not required [...] in patients with typical presentation of osteoarthritis.

Table 2.1: Osteoarthritis Guidelines

Planar radiography has been the tool most studied in this capacity. The hazard ratio of radiographic hip OA for incident THR over 11–28 years was 12.9 (95% CI 7.9–21), regardless of symptoms.[203] The grade of radiographic hip OA at baseline was, by far, the strongest predictor of clinical progression or progression to surgery over 7 years with the OR for THR increasing from 6 (all-comers, irrespective of baseline pain) to 24 (95% CI 11–52) in those having both pain and radiographic OA at baseline. Why has downplaying the predictive value of radiological OA hip features become widespread?[109] It seems clear that older patients will have hip pain for many reasons (trochanteric bursitis, soft tissue or

referred pain) unrelated to radiographic appearances, and equally clear that some patients will tolerate OA changes in the hips without needing surgery due to differing pain perception or patient/surgeon inclination.

2.2 Introduction

I started by scoping Osteoarthritis guidelines from the last 3 years (2014-2017) that were based on valid systematic literature review (SLR), and that gave specific evidence-based recommendations concerning the role of imaging in the management of hip osteoarthritis in adults. My Population Intervention Comparator Outcome (PICO) components were Population [in older adults], Intervention [does imaging], Comparator [compared with no imaging or symptoms alone] and Outcome [have utility in the primary management of hip osteoarthritis, in particular, the selection of patients to refer for total hip replacement surgery]. I sought documents in the public domain that based practical recommendations concerning the use of hip imaging on SLR, involved relevant expert consensus and were accredited. Five current guideline documents met the criteria, Recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis from the European League Against Rheumatism (2016), Osteoarthritis Tool from the Arthritis Alliance of Canada/ Centre for Effective Practice (2017), ‘Pain Arising from the hip in Adults’ (2017), from the Royal College of Surgeons (RCS, 2017), Quality Standard QS87 (2015), and Osteoarthritis care and management Clinical Guideline CG177 (2014) from NICE (2015). In total, 4 guidelines deter clinicians from ordering radiographs for hip osteoarthritis. EULAR advise against imaging any joint in a patient presenting with pain, namely, “Imaging is not required [...] in patients with typical presentation of osteoarthritis”. This is also the position of NICE who add that “the results of X rays and scans do not explain symptoms or help when deciding about treatment” and comment that their recommendations “[...] reduce both potential harm from exposure to radiation from X rays and costs of unnecessary imaging [...]”. While the Osteoarthritis Tool states, “Radiography does not reliably correlate with symptoms,” the guideline reserves X-ray only for patients with advanced hip disease by clinical examination. In contrast, the 2017 RCS recommendations (2017) state “a plain AP radiograph of the pelvis may be requested to confirm the diagnosis after history and examination” and advise surgeons to consider total hip replacement in 4 instances, including when “there is narrowing of the joint space on radiograph”. I investigated the strength of these recommendations by

evaluating the clinical utility of hip pain and various imaging parameters in confirmatory case finding (that referral for total hip replacement would be appropriate) and reassurance (that surgical referral would be unnecessary).

2.2.1 Radiographic Features Of Hip Osteoarthritis

A joint with a recognised severe radiographic change is more likely to be painful than those with a mild or no change at all.[204] Individuals who require THR for osteoarthritis have strongly associated hip pain symptoms and radiological changes.[205] Individuals with radiological signs of hip osteoarthritis have restricted hip movement,[206] confirming that function is correlated with radiological osteoarthritis, see *Figure 2.1*.

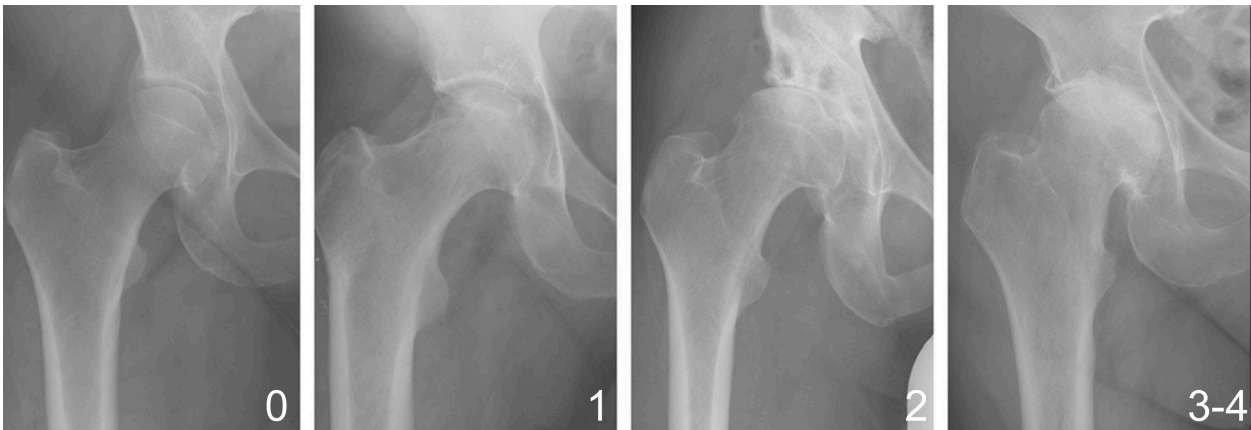


Figure 2.1: Radiographic Features Of OA.

Image adapted from [207]

The four most common radiographic features of hip osteoarthritis, see *Figure 2.2*.

- i) reduction of the space between the femoral head and acetabulum ($<$ joint space width)
- ii) visibly denser area of bone just under the cartilage of the joint (subchondral sclerosis)
- iii) formation of a fluid-filled sac that extrudes from the joint (subchondral cyst formation)
- iv) outgrowths of bone tissue forming around damaged joints (osteophytosis)

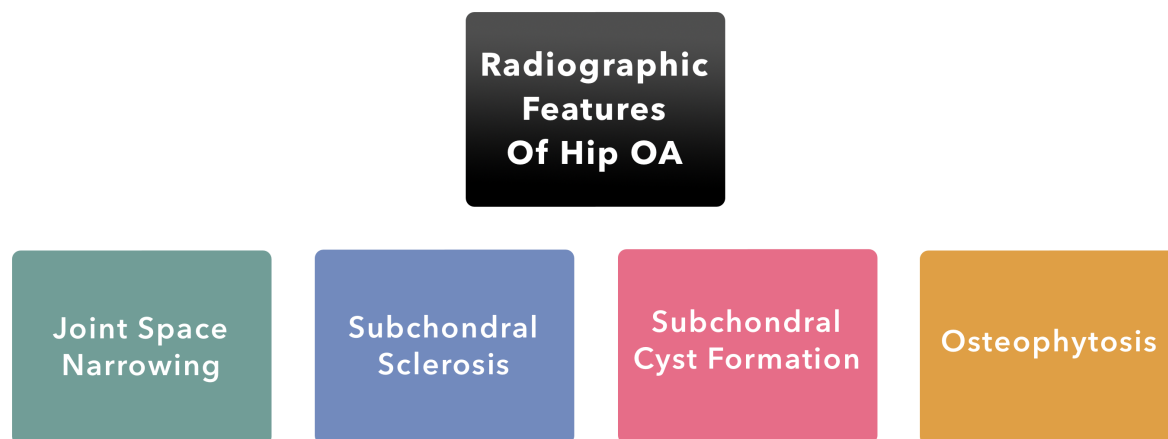


Figure 2.2: Radiographic Features Of OA

Joint Space Narrowing

When the loss of cartilage in an individual with osteoarthritis begins, it is commonly focal and dominates sites of heavy weight-bearing joints such as that of the hip. Focal thinning of cartilage manifest by JSN is an important observation that radiologists look for to differentiate osteoarthritis from other arthropathies, such as rheumatoid arthritis.[208]

Subchondral Sclerosis

As osteoarthritis onset progresses, changes occur in the thickness of the cartilage which lead to an increase in the transmission of forces of maximal stress on the subchondral bones of a joint. These bones naturally respond by increasing local blood flow[208] and increase bone density or thickness. However, basic research into OA mechanisms is highlighting the fact that subchondral bone thickening may in facet precede overlying cartilage loss. Trabecular microfractures may begin to occur creating a radiographically visibly denser area of bone under the cartilage.

Subchondral Cyst Formation

Cysts typically occur in osteoarthritis but are also seen in other arthropathies as fluid-filled sacs that extend from the joint. Radiographically they occur at sites of increased pressure transmission and joint stress. It has been suggested that pressure induced intrusion of synovial fluid may cause cystic lesion growth.[209, 210]

Osteophytosis

Osteophytes are outgrowths of bone that commonly occur at the margins of osteoarthritis joints. They are clearly visible and can be easily identified by radiologists. The spurs themselves are not painful, but collision with nearby structures such as periosteum, can cause pain with movement.

2.2.2 Methods Of Radiographic Assessment Of Hip Osteoarthritis

Radiographic osteoarthritis has been the preferred definition of incident osteoarthritis in the majority of large cohort studies. Radiographic definitions are usually based on the Kellgren and Lawrence (K&L) system which grades (on a score out of 0-4) the extent of radiographic osteoarthritis, see *Table 2.2*.

K&L Score	Classification	Feature Description
0	None	No radiographic features of osteoarthritis
1	Doubtful	Possible JSN and osteophyte formation
2	Mild/Minor	Definite osteophyte formation and/or JSN
3	Moderate	Definite osteophytes, definite JSN, sclerosis, cysts and possible bony deformity
4	Severe	Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Table 2.2: K&L Grading System

It scores no disease as zero, and as the numbers increase up to four, so does the subjective worsening of the disease. The scoring is based on the presence of certain key severity features, such as accumulation of osteophytes and the space between the femur and acetabulum known as the joint space width.[211, 212] The anatomy of individuals may vary, therefore relying solely on radiographic findings in osteoarthritis is not always ideal as they do not always correlate with clinical symptoms. Thus, some studies which use only the radiographic definition of osteoarthritis may not include patients with clinical disease. Just as, solely relying on radiographic findings is not recommended, one should not solely rely on clinical symptoms. Incorporating qualitative radiographic techniques, as well as clinical joint rotation analysis and pain identification are key for more accurate and reliable osteoarthritis classification.

This K&L grading system continues to be used by researchers today. Criticisms of the system are directed at the emphasis on the osteophyte, the subjective grades of severity from normal to severe (0–4), and that the system is relatively insensitive to changes. There are also concerns over inter and intra-observer variability, hence it is not used routinely in clinical practice. A comprehensive study was carried out by Reijman et al. where the group investigated seven different measures of hip osteoarthritis.[213] They came to the conclusion that minimum joint space width (mJSW) demonstrated the highest measurable reliability.

Joint space width (JSW) is a useful measurement for the radiographic assessment of hip

osteoarthritis thickness of articular cartilage. JSW measurement in standing assesses compression (under load) of cartilage, and its material thickness.[214] Measurements of the mJSW are taken at or close to the side of load transmission in a joint. It is defined as the smallest measurable distance between the acetabulum and the femoral head.[215] The distance should normally be 2–3mm.[216–218] If a smaller distance than 3mm is measured, this is an indication of radiological osteoarthritis.

When studies involve radiographic investigations of the hip, there are certain technical considerations such as accurate positioning and image acquisition orientation. The most common radiographic method is the AP view where the hip is internally rotated. Other views such as the cross table or frog leg lateral views require the hip to be flexed and externally rotated to ensure that the X-ray beam could be directed posteriorly. On the AP radiograph both, the greater and lesser trochanter, should be clearly visible and defined; the greater trochanter should also not overlap the femoral neck. There should not be excess external or internal rotation as both may impact on JSW measurements. The Lesquesne's[219] view (patient is standing) with an assessment of JSW may be useful for early osteoarthritis identification. It is an oblique view of the acetabular edge, thus able to diagnose if osteoarthritis is affecting the anterior part of the hip joint. The Lesquesne's view is also useful to measure the femoral head's anterior coverage.

When radiographs are acquired, patients may be either in a supine position or standing. Theoretically, a standing radiograph may provide a more accurate estimation of cartilage thickness because it realistically recreates the weight-bearing condition the hip is naturally found in,[220] accurate measurements of hip JSW can be obtained on both supine and standing radiographs.[221–223] An exception of JSW assessment is patients with hip dysplasia, where standing radiographs generally provides more accurate results.[224] Supine radiographs have been shown to provide more accurate assessment of JSW in obese patients because there is less abdominal pannus projecting over the hip joint limiting X-ray beam penetration.[221] So the most appropriate scan position depends on the what is best for the individual being assessed.

If the subject is supine, the feet should be internally rotated 15-20 degrees and the X-ray beam should be perpendicular to the table and centred on the superior area of the symphysis pubis. This positioning will generate enough force on joint to mimic weight-bearing.[225] It

is not always easy to get patients to accurately lay with a 15-20 degree for the duration of the entire scan, so assistive positioning devices are often used.[221] If the subject is standing then both feet should be internally rotated by 10 degrees for the scan.[133]

Spine CT images can be used to create digital reconstructed radiographs (DRR) which are very similar but subtly different from the standing 2-view plain radiographs used in routine clinical practice; hence our cut-off values of mJSW cannot be applied to ordinary radiographs. This modality of imaging will be extensively studied in the methods section.

How well does mJSW predict THR?

Few studies have investigated the predictive validity of different metrics of hip mJSW for clinical outcomes. Liu et al. investigated how well 3D mJSW, over time, predicted or was associated with subsequent THR.[226] They noted that all JSW loss metrics were significantly associated with THR within 48 months, demonstrating the strong predictive validity of hip JSW change for subsequent THR. In other studies, however, radiographic mJSW has been shown to vary significantly within the joint itself.[218] This in itself raised questions as to exactly where JSW measurements should be made.

How well does mJSW predict pain?

Numerous studies and systematic reviews have been conducted to better understand how well mJSW predicts pain, and if people with pain have a significant change in their mJSW.[227] In a population-based investigation of 3595 participants, the presence of hip pain was associated with mJSW.[213] In a separate population-based study with a similar number of participants (3208), a mJSW of $\leq 2\text{mm}$ was significantly associated with self-reported pain over a period of 12 months.[228] A study of 220 subjects with hip pain of $\geq 3\text{months}$ found an association with a mJSW $\leq 2.5\text{mm}$. [229] A study of 759 men (60-75 y/o) identified hip pain as associated with a reduced mJSW.[230] In a cohort of 195 subjects, a mJSW of $\leq 2.5\text{mm}$ was predictive of being put on a waiting list for joint replacement.[231] In a study of 224 subjects ($>50\text{ y/o}$) with hip pain, a joint space of $<2.5\text{mm}$ was also predictive of eventual THR.[232] Overall, most studies that have been reviewed suggest that, in the general, population and in subjects with hip pain, there is an association between reduced mJSW and THR, therefore a mJSW of $\leq 2.5\text{mm}$ appears to be the accepted diagnostic level for mJSW.

The Outcome Measures in Rheumatology (OMERACT) is an independent initiative of a committee of health professionals interested in outcome measures in rheumatology. They have been responsible for the development, validation and implementation of clinical and radiographic outcome measures in osteoarthritis and other rheumatic diseases.

What does OMERACT say about mJSW?

The objective of the OARSI-OMERACT initiative[233] was:

“...to define a cut-off evaluated in millimetres on plain X-rays above which a change in JSW could be considered as relevant in patients with hip osteoarthritis...”

Table 2.3 summarises the consensus based on expert opinion of a panel of researchers after reviewing the results of systematic literature searches. There was a broad consensus for the cut-off values of 0.22-0.78mm on plain X-rays above which a change in JSW could be considered as relevant in patients with hip osteoarthritis. The committee also believe that the results of JSW analysis should be expressed in a dichotomous variable (progressors yes/no).

Definition	
1	Structural progression is optimally defined by plain radiological evaluation of JSW in millimeters.
2	The results of the analysis of JSW should be expressed in terms of a dichotomous variable (progressors yes/no).
3	An absolute change in JSW over a predefined threshold is defining a progressor.
4	The threshold above which a change in JSW can be considered as relevant should be based on the evaluation of the measurement error of the radiological technique.
5	The Bland and Altman technique [234] is the most appropriate one to evaluate the measurement error of the radiological technique evaluating JSW.
6	The pilot study aimed at evaluating the measurement error should be designed to reflect the different characteristics of the primary study in which the analysis of the radiological findings will be based on (patient’s characteristics, centers characteristics, readers ...).

Table 2.3: OARSI-OMERACT Definition Of Relevant Structural Progression In Hip OA

2.3 Medical Imaging Using Ionising Radiation

2.3.1 Plain X-Rays In The Evaluation Of Hip Osteoarthritis

X-rays of the hips for the evaluation of osteoarthritis include a standing AP pelvis view and frog-leg views of the suspected hip joint. On plain X-ray evaluation of an osteoarthritis joint, loss of the radiolucent cartilage results in JSN. However, it is also possible to get more central wear, particularly in patients with deep sockets or protrusio acetabuli. Subchondral sclerosis or an appearance of whitening of the subchondral bone is also often present in radiographic images of osteoarthritis. Osteophytes, which reflect a regenerative process with formation of fibrocartilaginous extensions at the joint margins, are common.[235] When osteoarthritis is identified on plain X-rays, it means that there is often substantial cartilage loss and sometimes full-thickness cartilage loss with bone-on-bone contact. Early osteoarthritis detection and identification are important in order to reduce the likelihood of progression to the bone-on-bone contact stage, which is inevitably painful and associated with loss of function.

2.3.2 Computed Tomography (CT)

Computed Tomography (CT) is a 3D X-ray absorptiometric measurement which provides the distribution of linear attenuation coefficient in a thin cross-section of tissue.[236] CT relies on a photon beam passing from an X-ray source, through a patient's body and detected on the other side by detectors, see *Figure 2.3*.

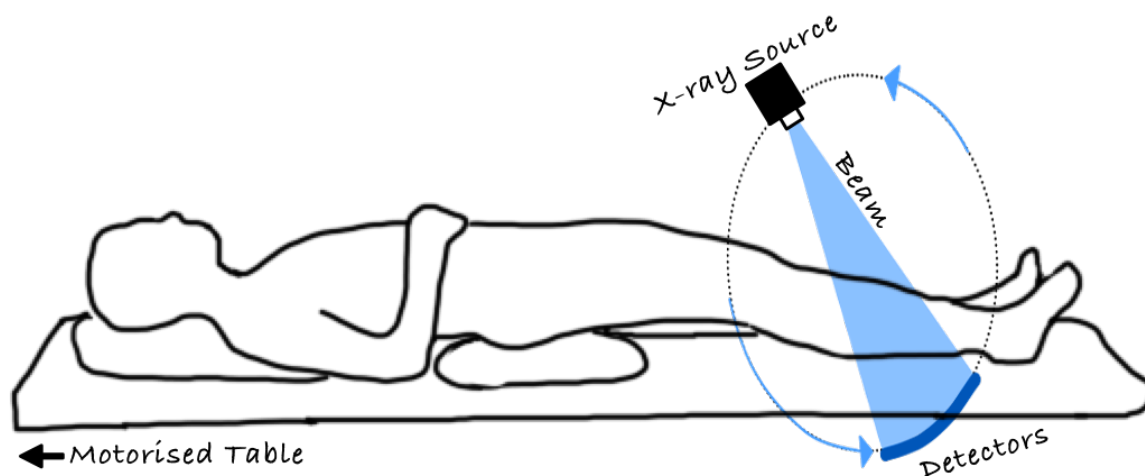


Figure 2.3: CT Beam Setup

In a typical acquisition period 10-50 rotations of the X-ray tube are made around a patient. Many different snapshot images are collected at different angles during one complete rotation. If the photon beam passes through a dense material (bone), it senses a fair signal, conversely, if the beam passes through air or tissues, the detector senses a strong signal (the quantified measurement of ease with which a material is penetrated by a beam is known as the attenuation coefficient), a computer then reconstructs all of the individual snapshot images into a cross-sectional image of the internal bone/tissue information and converts it into a set of images.

2.3.3 Multidetector Computed Tomography (MDCT)

Modern advances in multi-detector computed tomography (MDCT) have had a profound effect on imaging of bones and their adjoining muscles.[237] Machines which are regularly used in hospitals these days have unparalleled spatial resolution and incredibly fast scanning times making them ideally suited for the assessment of bone surfaces in both healthy and trauma patients. Some can even be used to check the integrity of already implanted orthopaedic hardware.[238] There are some very important basic concepts which must be understood when understanding musculoskeletal imaging: Magnetic Resonance Imaging (MRI), see *Section 2.4.2* has superior contrast resolution compared to CT, but CT can directly image both cortical and cancellous bone. CT has greater spatial resolution compared to MRI meaning that very small structures and details can be studied in detail. MDCT scanners are so fast that they can produce entire isometric (identical length, width, and depth image information) musculoskeletal image data sets in a manner of seconds. Isotropic images can be made (where all dimensions of the volume elements of an image are of the same size) allowing for high-resolution images to be produced in any plane, even after the initial images have been acquired.[239] A very significant downside to MDCT is the relatively high dose of radiation emitted. Numerous studies, however, have suggested slight modifications in the data acquisition process to reduce the overall dose, especially for paediatric patients.[240–242]

MDCT scanning systems, unlike older generation CT systems which generated a single photon beam, actually generate multiple photon beams simultaneously; they are sensed by a system of detectors after they pass through a patient's body, ensuring that multiple slices will be observed by a computer simultaneously.[243] This type of system gives absolute freedom for a radiographer to adjust detector arrays as necessary; for example, increasing or reducing

the slice thickness (as thin as 0.5mm). This also means that the X-ray beam could be used more efficiently than older CT systems, see *Figure 2.4*, reducing the radiation dose and increasing the axis or rotation and therefore capturing more slices in with less radioactive damage to cells.[244]

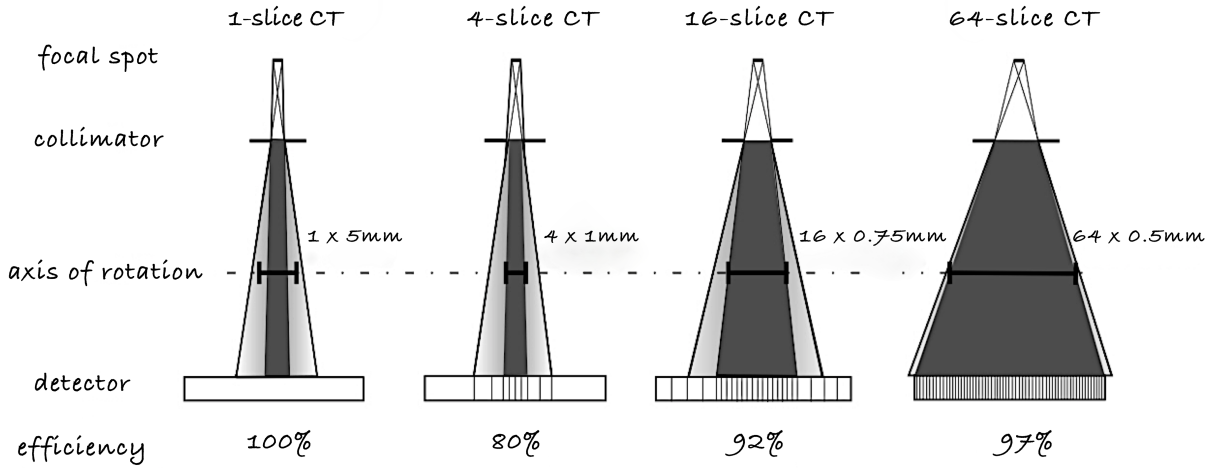


Figure 2.4: Efficient Use Of X-ray Beam By Increasing Slices And Reducing The Radiation Dose Compared To The Same Number Of Slices Acquired Using Plain CT

2.3.4 Hounsfield Units

A computer that is attached to the scanning system generates MDCT image data sets, the images produce various attenuation values of tissues, and these values are measured in what are known as Hounsfield units (HU), see *Equation 2.1*.

$$HU_s = \left(\frac{\mu_s - \mu_w}{\mu_w} \right) \times 1000 \quad (2.1)$$

The HU value for any material is defined by *Equation 2.1*[245]

Where HU_s = The HU value for substance, s

μ_s = Linear attenuation coefficient for substance, s

μ_w = Linear attenuation coefficient for water, w

Air, which has very *low* density, has extremely low HU values. Tissues such as fat and muscles have *intermediate* values of density and therefore intermediate HU values. Bone has a very high density and therefore it has *high* HU values. Air measures -400 to -600 HU. Intermediate tissue like muscle has typical values of 40 to 80 HU. Fat (less dense than muscle) has typical values of -60 to -100 HU. Cortical bone (outside of bone) typically has values in the region of 400 to 1000 HU. Dense cortical bone has typical values of 1600 HU. Cancellous bone (spongy inside of bone) has values of 100 to 300 HU.[246]

2.3.5 Quantitative Computed Tomography (QCT)

Quantitative computed tomography (QCT) is a medical technique that is used to measure the bone mineral density (BMD) using a standard CT scanner with a specific calibration standard in order to convert the HU of the CT image to bone mineral density values.[247] QCT enables the accurate quantification of 3D bone geometry and the accurate estimation of volumetric bone mineral density (vBMD).[236] A typical QCT involves solid phantoms (used for calibration) to be placed under the patient (usually attached to a belt) during the CT image acquisition stage. Phantoms contain specifically chosen materials to represent a variety of bone mineral densities. The most commonly used phantom materials, used as a reference standard, are Calcium Hydroxyapatite (CaHAP) and Potassium Phosphate (K_2HPO_4); however, it is common that each manufacturer has their own phantoms to fit their own machines. QCT enables the application of finite element modelling (FEM), which is a numerical engineering technique that enables a computational estimation of the effects on a bone when subjected to an external load. QCT, however, is not able to provide high-spatial resolution images to quantify the trabecular bone microstructure due to the high dose of radiation required to acquire such detail.[248]

2.3.6 Peripheral QCT

Peripheral quantitative compound tomography (pQCT) is a technique used to measure the internal bone geometry. The X-ray source and detector rotate around a patient generating 1-2mm thick image data sets. Specific phantoms (usually hydroxyapatite) provides a measurement of the vBMD: this ensures that it is independent of bone size. This method provides a quantified assessment of the internal geometry of bone.[249] pQCT alone does not measure BMD, but it can be used together with quantitative ultrasound as peripheral methods of analysis.[250] It is not suitable for in-vivo measurements of the hip (only forearm and tibia) but is highly useful for evaluating ex-vivo cadaveric hips.[251–256]

High resolution pQCT (HR-pQCT) is a technique which measures the vBMD, trabecular and cortical micro-architecture of the distal radius and tibia with an isotropic resolution.[257] HR-pQCT acquires patient images based on the same principles as standard QCT but it can achieve a much higher resolution set of data; a disadvantage is that there is a smaller field of view (an isotropic voxel size of $82\mu m$).[258] This permits only the scanning of peripheral sites

of bones. Previous research conducted by Nishiyama et al. 2013 has suggested that average scans take 2.8 minutes to acquire an axial 9.02mm section in the only currently commercial system available to the market (XtremeCT; Scanco Medical, Brüttisellen, Switzerland).[259]

2.3.7 CT Safety

Modern MDCT systems have significantly reduced patient radiation doses[260] compared to the previous generation single-beam CT systems because they now have more efficient beams and less scatter per slice when looking at the same parameters for a typical scan. However what also needs to be considered when investigating radiation dose in the modern MDCT systems is that they generally create more slices per scan with much more overlap than the older generation systems: this essentially increases the dose.[261] After thorough investigation by the FDA, it was determined that a typical CT scan of a patients head produces an effective dose of 2.0 millisieverts (mSv), and a typical CT scan of a patients abdomen produces an effective dose of 8.0mSv.[262, 263] The time period for the equivalent effective dose from natural background radiation is 2.7 years, where they based the assumption of an average “effective dose” from natural background radiation to be 3mSv per year in the United States. The values of 2mSv and 8mSv are comparable to 100-500 frontal-view chest X-rays. Therefore, the FDA suggests that one standard CT examination with an effective dose of 8-10mSv could increase the possibility of fatal cancer of 1 in 2000 people.[264] Dedicated pQCT scanners use the old systems of CT technology (rotation and translation); it is very slow to acquire image data, and each section takes about 1 minute to attain. The radiation dose from central QCT is higher than Dual-Energy X-Ray Absorptiometry (DXA) (effective dose is 1 to 6mSv), however, this compares favourably when looking at something like a lumbar spine radiograph (effective dose is 700 to 1000mSv).[265] By using a low kV radiation dose, the dose for QCT will be approximately 90mSv. A low kV value is important in this case because most of the scattered radiation, which is generated at the start of an X-ray beam, does not penetrate the body; at higher kV values, however, the scattered radiation passing through the body contributes more to adverse effects. Compared to central QCT the dose from pQCT is extremely low (less than 0.5mSv).[266]

2.4 Medical Imaging Using Non-Ionising Radiation

2.4.1 Dual X-Ray Absorptiometry (DXA)

Although classically a tool to diagnose osteoporosis and predict hip fracture, recent studies pinpoint a role for structural measures by Dual X-Ray Absorptiometry (DXA)[267] and density measures by DXA[268] in predicting hip OA and outcome. A DXA scan is most commonly used to determine bone health. The test measures bone mass at the axial and appendicular skeleton. It can be used to diagnose osteoporosis, determine chances of a fracture occurring and measure a person's response to ongoing osteoporosis treatment.[269] DXA technology is the commonest in routine clinical use to measure BMD.[270] This imaging technology is usually applied to the hip and spine.[271] It measures the attenuation of photons of two different energies, allowing for the determination of whether it is bone or soft tissue; photons with high energies are attenuated by bone, thus photons with low energies are attenuated by soft tissues. Common features that DXA system printouts include are a summary of patient demographics, image of the scanned skeletal site, a plot of patients' age versus BMD, and various numerical results. Correct positioning and data output of a DXA scan, see *Figure 2.5*, the hip is internally rotated in order to make the lesser trochanter not apparent to optimise the femoral neck analysis, the black lines are used for reference, the large rectangle is used to show the region of interest and the small square is the Ward's triangle region of interest.

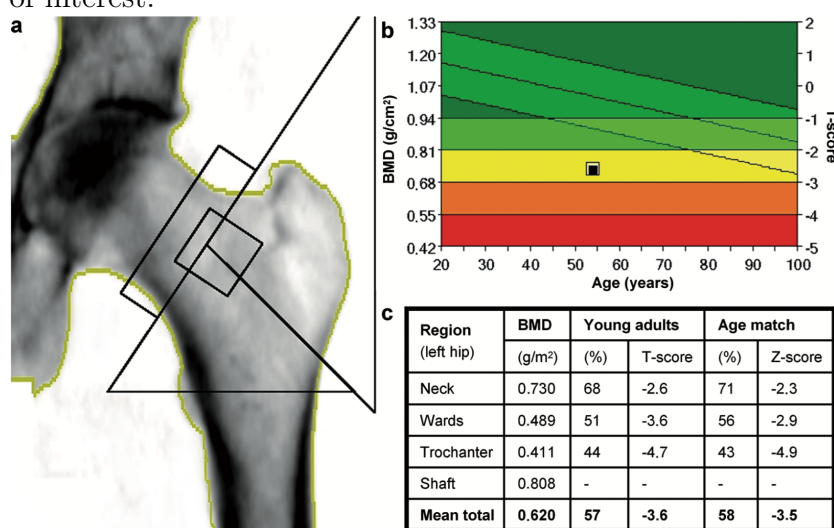


Figure 2.5: Typical DXA results and interpretation. a) Dual-energy X-ray-absorptiometry (DEXA) of the left hip. b) T-score of -2.6 (black square) for the neck of the femoral bone (bone mineral density: BMD). c) Results of DEXA showing BMD, T-score, Z-score and percentage compared to indicated reference population (young adults, age match) at different regions of the left hip and mean values[272].

2.4.2 Magnetic Resonance Imaging (MRI)

MRI measures the spatial distribution of specific nuclear spins of protons in the body. Electrical signals from the spins are measured using precessional motion (change in the directional axis of a rotating object) of the proton spins after getting excited by radio-frequency (RF) pulses, which are irradiated in a constant static magnetic field. The electric signals in a static magnetic field are known as nuclear magnetic resonance (NMR). NMR itself doesn't carry spatial information that is necessary to generate an image. Gradient coils are used to generate spatial information. Pulsed electric currents drive these gradient coils in a strong magnetic field. Such strong forces acting on the coils in this repetitive manner are responsible for the production of the stereo-typically loud sounds heard during an MRI scan. MRI is able to evaluate both the structure and the thickness of articular cartilage. MRI can detect large focal articular cartilage lesions that cannot be detected on plain films.[273, 274]

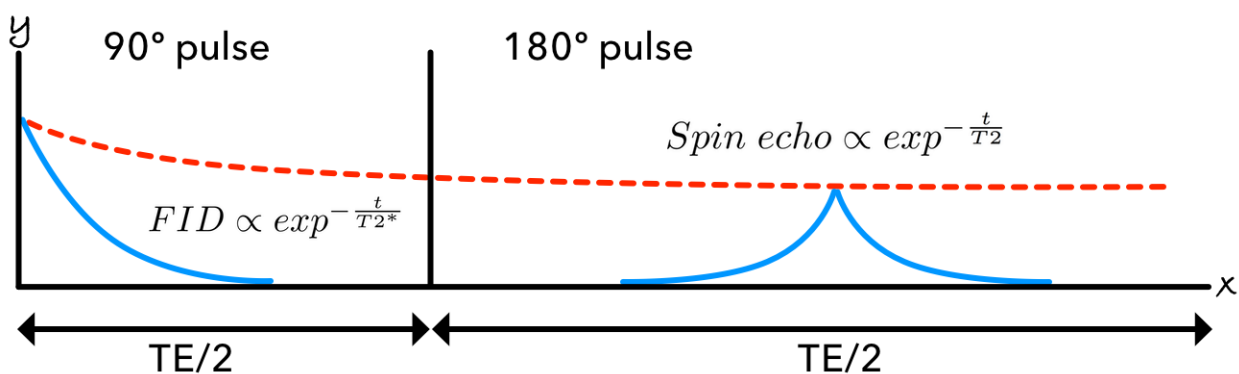


Figure 2.6: Graphic representation of FID and spin echo for a typical MRI scan. Spin echo signals decay exponentially. T2 is the relaxation time and it represents the time constant of this decay curve. The faster decay due to non-uniformities in the magnetic field is known as the FID with a time constant of T2*

As *Figure 2.6* shows in the graphical representation, there are two types of NMR signals used in MRI: free induction decay (FID) and spin echo.[275] FID is produced by one RF pulse, it decays with a time constant T2*. At a specific echo time (TE), TE/2 after the second RF pulse, the spin echo signal is observed, its signal decays with a time constant T2.

The most important parameters of MRI are the proton spin relaxation times, the convention used are: T1, T2 and T2*.

T1 is the longitudinal relaxation time, this is the duration that it takes the nuclear spins to return to a thermal equilibrium post RF pulse irradiation. T1 is used to visualise the degree of saturation of the NMR signal. Equilibrium magnetisation is reinstated by T1 relaxation, it happens quickly for fat but more slowly for water.[276]

T2 is the transverse relaxation time, this is the lifetime of spin echo signal. T2 is used to distinguish normal tissues from pathologic tissues because the “proton spins” of pathological tissues generally have longer values of T2. When magnetisation is formed in the transverse plane, it decays exponentially with T2 relaxation: again this happens quickly for fat but more slowly for water.[276]

T2* is the decay rate of the FID signal. This means that tissues with a long T1 are dark on T1-weighted images, and tissues with a long T2 appear bright on T2-weighted images.

MRI can now be used to evaluate abrasions of the articular cartilage. Early studies have suggested that the T1 and T2 weighted images are incredibly useful for the study of articular cartilage degeneration in diseases like osteoarthritis.[277] A variation of classic MRI known as magnetisation transfer contrast (MTC) imaging can separate articular cartilage from adjacent joint fluid in its images by suppressing the signal produced from cartilage.[278, 279] Driven equilibrium Fourier transform (DEFT) imaging has provided contrast between joint fluid and the cartilage around it by improving the signal generated from the joint fluid, rather than suppressing the signal from cartilage tissue as other technique do.[280] It has been suggested that the signal intensity of articular cartilage not always be uniform due to a number of internal factors which cannot always be controlled so the appearance of articular cartilage is highly variable,[281, 282] it is, therefore, important to improve diagnostic accuracy in order to reduce the risk of misdiagnoses.[283]

MRI has great potential to be more sensitive than both plain films and ultra-sonography in the detection and grading of hip osteoarthritis. Of the current 3D imaging methods in use today, MRI is used most commonly for hip osteoarthritis, as evidenced by scoring systems such as the Hip Osteoarthritis MRI Scoring System (HOAMS) score, however, it is not as useful as MDCT for accurately defining the bony features.[284]

2.4.3 MRI Safety

MRI is a non-invasive system: it does not involve radiation (unlike CT). The main caution is the effect of the strong magnetic field on magnetic metal objects or potential implants a patient might have, such as pacemakers, metallic clip, some artificial valves, and jewellery. In some cases metal objects may be permitted, provided that they do not disrupt the image of the area under investigation, but patients are very rarely permitted to MRI scans if they have pacemakers, metal in eye, otic implants or cardiac defibrillators. There have been cases when patients have died during an MRI examination,[285] so it is very important that care is taken when deciding if a patient can and cannot have an MRI scan. Patients with tattoos are also suggested to press icepacks onto the tattooed areas decreasing the potential for RF heating.[286]

2.4.4 Ultrasound

Ultrasound is an established imaging technique that helps with early diagnosis and follow-up of rheumatologic issues and conditions. Its relatively cheap cost to run means that many more health centres can afford to buy ultrasound machines than MRI machines and unlike CT, no ionising radiation is involved, so no expensive radiation insulating rooms need to be built.

Ultrasound imaging proves to be an essential initial point of investigation for real time evaluation of many patients when they complain about internal discomfort. It is generally the first tool doctors use to look at a patients soft tissues, blood flow assessment and bones but cannot identify bone marrow edema.

Ultrasound images also known as sonograms are produced by sending a pulse of ultrasound, typically in the frequency range of 1-18MHz into tissue using an ultrasound transducer. The sound travels into the patients' skin and reflects from parts of the tissue inside according to the Doppler Effect; these signals travel back to the transducer and are recorded by a computer to be displayed as an image to the operating clinician.

Current ultrasound systems are capable of resolving power of less than 0.1mm, this is not even possible by MRI or CT.[287, 288] This high resolution is however not necessarily very good at tissue penetration, therefore, ultrasound systems cannot image tissues at the same depths MRI or CT are able to.

Thinning of cartilage and the loss of joint space have been observed using ultrasound,[289, 290] however, such sonographs may be unreliable when small joints are being observed due to transducer probe size limiting factors; therefore, the diagnostic accuracy relies heavily on the experience of the sonographer and technology being used and must be studied with caution. Weinrauch et al. recently described the use of ultrasound assisted hip arthroscopy (in more than 700 procedures) as a simple and easily reproducible technique to manage central and peripheral-compartment procedures. This reduced their need for fluoroscopy down to 2% of the time.

Typical imaging features of interest in osteoarthritis are JSN, subchondral sclerosis and subchondral cyst formation; therefore, radiographs still remain the standard for diagnosis, however, this is not to say that ultrasound cannot be used to some extent, see *Figure 2.7*. Ultrasound systems are better at quantifying cartilage loss in large joints such as the knees and shoulders, which are close to the surface of the skin.

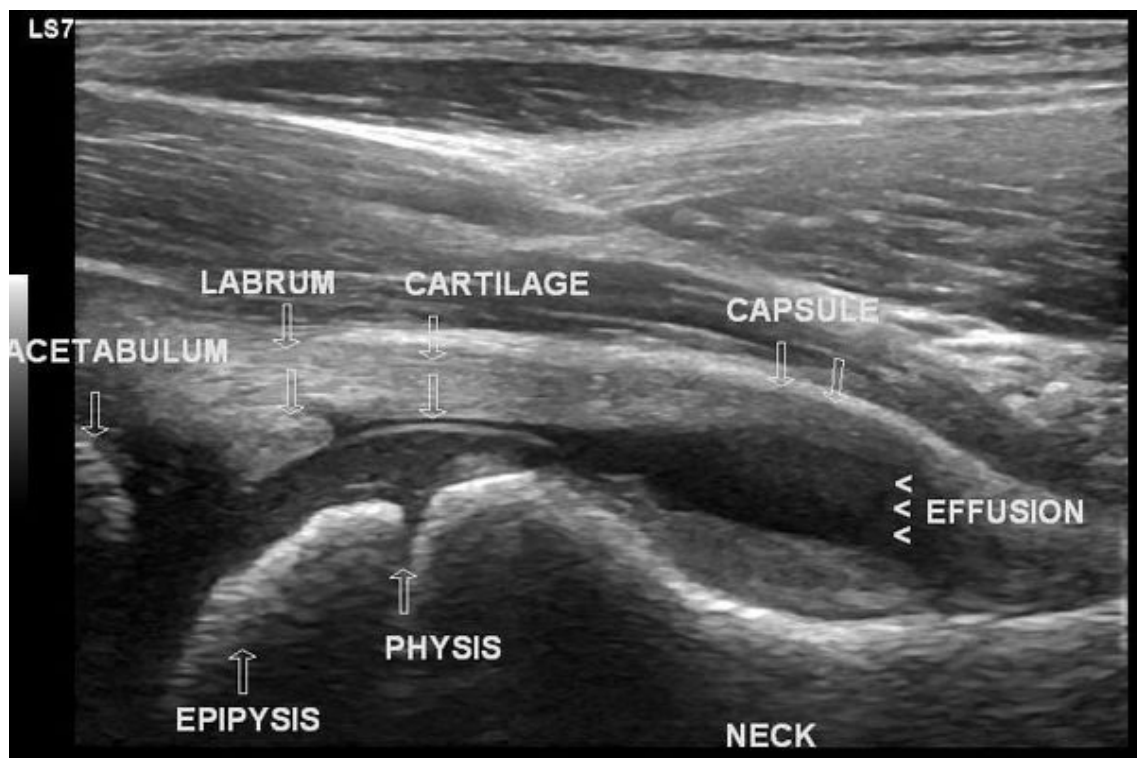


Figure 2.7: Hip Ultrasound Image

Image From https://images.radiopaedia.org/images/26775861/4b26dd0b950468b0892d710f1eb8b8_big_gallery.jpeg On 23rd June 2018

2.5 Selecting An Imaging Technique For Hip OA Research

When considering the different imaging systems available it is important to understand the advantages and disadvantages of using each system both in a research and clinical sense. In *Table 2.4* the advantages and disadvantages of each of the techniques are evaluated. MDCT is clearly the standout technique because my research needs to quantify bony features in 3D.

Imaging System	Advantages	Disadvantages	Average Radiation
MDCT*	1. With appropriate scanning parameters, can produce extremely accurate high-resolution images very fast. 2. Can evaluate internal derangement. 3. Compared to CT same acquisition in shorter time (fewer motion artefacts).	1. High radiation dose. 2. Some imaging artefacts (although better than single slice CT). 3. Can produce 3D images, but costly software usually required.	2mSv for a head exam 8-10mSv for abdomen exam
HR-pQCT*	1. Size independent. 2. Low radiation. 3. Measures bone geometry and strength. 4. Very detailed images of high resolution quality ($80\mu\text{m}$).	1. Long scan times. 2. Sensitive to movement. 3. Used for peripheral sites (not hip). 4. Imaging artefacts often present. 5. Expensive equipment.	$<3\mu\text{Sv}$
DXA*	1. Rapid scan time. 2. Low cost. 3. Low in ionising radiation. 4. Used in OA research mainly for hip shape analysis.	1. Size dependent measurements (low resolution). 2. Software and reference data changes. 3. Unable to quantify JSW, cortical thickening, trabecular bone characteristics.	$<1\mu\text{Sv}$
MRI	1. Radiation free. 2. Generally painless and harmless. 3. Excellent imaging detail. 4. When necessary MRI contrast agents (normally gadolinium) are less allergenic than CT contrast agents (iodine-based).	1. Long scan times, difficult to lay still for +30 minutes for patient. 2. Not suitable with metal implants. 3. Can cause heart pacemakers to stop functioning. 4. Does not show bony features well.	N/A (uses powerful magnets instead of radiation)
Ultrasound	1. Radiation free. 2. Provides some basic bone density and some structural information. 3. Safe, portable equipment, easy to use. 4. Most inexpensive imaging system.	1. Difficulty to compare the results obtained with those acquired by X-ray. 2. Same images are hard to replicate. 3. Hip ultrasound is highly operator dependent (skill required).	N/A (uses ultrasound sound waves)

*Commonly used for bone measurements

Table 2.4: Summary Of Typical Imaging Systems Used

Chapter 3

Materials And Methods

In this chapter, I will discuss the methodology of three studies, the results of which will be reported in detail in Chapter 4.

The studies are:

- (a) The Age, Gene/Environment Susceptibility-Reykjavik (AGES) Study – a study to predict THR and hip pain in women and men
- (b) The 3D Printing Study – a study to visualise the cortical thickening in osteoarthritis and how it relates to the whole joint structure
- (c) The Mindways Study – a study to understand how osteoarthritis-prone parts of the femoral head cortex change with age in women

3.1 Methods Of The AGES Study

3.1.1 AGES Study Hypothesis

Hypothesis 1: 2D imaging will have clinical utility in predicting hip replacement in those with hip pain.

Hypothesis 2: The 3D distribution of cortical bone thickness around the proximal femur will predict hip replacement in those with hip pain.

3.1.2 Background

Given the strong association between radiographic osteoarthritis and clinically meaningful outcomes (THR and radiological progression), I set out to apply modern 3D imaging methods to discover any characteristic radiological osteoarthritis phenotype that may be associated with subjects progressing to THR. I investigated the positive clinical utility of hip pain and various imaging parameters in confirmatory case finding (for total hip replacement referral) and negative clinical utility of imaging in reassurance (that surgical referral would be unnecessary). Using a large, prospective, nested case-control study, I investigated standard imaging measures (such as mJSW and osteoarthritis grade[291]) alongside 3D computed tomography measures[292, 293] of osteoarthritis as well as their association with hip pain, to evaluate how well structural measurements at the hip predict incident THR in a normal representative ageing Icelandic population of older men and women.

3.1.3 Study Population

Participants were volunteers in the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik study), a single-centre prospective population study of Icelandic women and men, initiated in 2002. The AGES-Reykjavik study was designed to study how various risk factors, such as genetic susceptibility and gene/environment interaction affected disease and disability in older age. It was a multidisciplinary study that provided detailed phenotypes of cardiovascular, musculoskeletal, and neurocognitive systems as well as an examination of body composition. The AGES-Reykjavik sample is drawn from an established population-based cohort, the Reykjavik Study. This cohort of men and women born between 1907 and 1935 has been followed by the Icelandic Heart Association since 1967. Further design and recruitment have been described in detail.[294]

“AGES-Reykjavik is based on three general hypotheses: first, that genetic variation contributes to disease occurring in old age; second, that selected diseases common in old age share genetic, behavioral, and environmental risk factors; and third, that better classification of phenotypes based on multiple streams of data, including midlife history and subclinical disease, will further the exploration of how these risk factors are associated with complex traits and diseases manifest late in life.”[294]

Discharge records from all hospitals performing THR surgeries in Iceland were examined. Cases were reviewed by a rheumatologist with expertise in osteoarthritis, who confirmed from medical records that the operation was carried out for osteoarthritis only, see *Figure 3.1*. Baseline assessment was extensive, involving pelvic CT and included hip pain specific (WOMAC Osteoarthritis Index) questions from the AGES-Reykjavik questionnaire which included health history, lifestyle practices and medication survey.

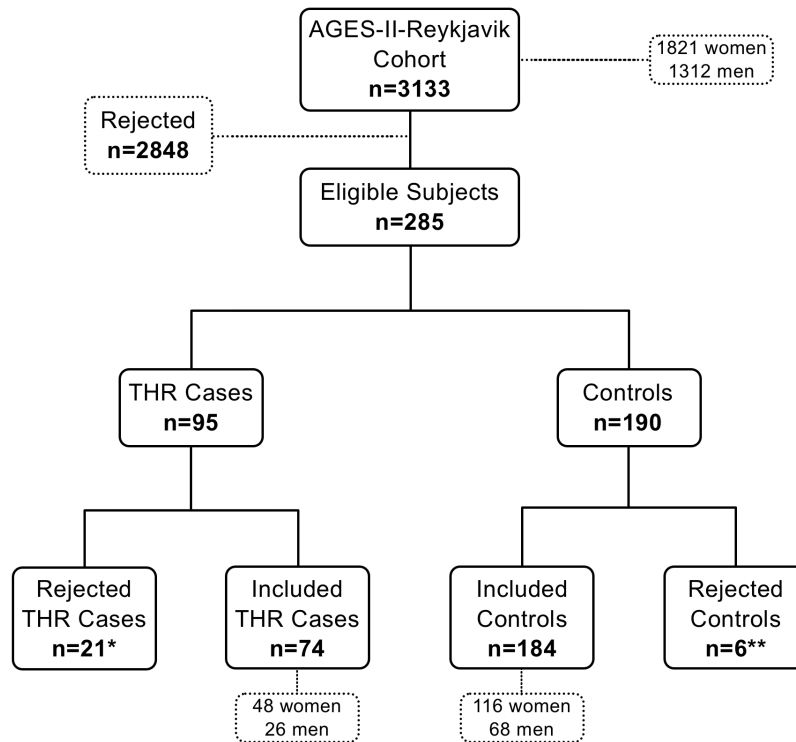


Figure 3.1: Schematic Of AGES Study Subject Selection, Inclusion And Exclusion Criteria

During an average five-years of follow-up of 3133 participants (with baseline pelvic CT scans between 2002 and 2006), 95 THR were reported. Of the 3133 participants, 2848 were excluded for the reason that they were not individuals who underwent future THR, they also did not match as controls to those participants who did go on to have THR. Using a random selection procedure, at least two controls were matched to each THR case matched for calendar year of recruitment, sex and age. Finally, osteoarthritis cases were arbitrarily split into atrophic and hypertrophic on the basis of their osteophyte count[2] (<10) to examine whether imaging findings associated more with one type or another. All participants provided written informed consent, and the study was approved (VSN 00-063) by the National Bioethics Committee in Iceland as well as the Institutional Review Board of the Intramural Research Program of the National Institute of Aging.

The full protocol for this imaging sub-study was considered and approved by the Icelandic Heart Association steering group. 21 of the case subjects were rejected: 18 subjects went on to fracture their hip but not due to osteoarthritis, 2 subjects had incomplete scans and 1 subject had motion artefact in the femoral shaft and neck. After the 21 cases were rejected, 74 subjects remained (48 women and 26 men), with 90 THR sides (16 subjects had bilateral THR). 6 of the control subjects were rejected: 4 subjects had motion artefact in the femoral shaft and neck, 1 subject had an incomplete scan, 1 subject presented with an unreliable phantom density value. After the 6 controls were rejected, 184 subjects remained (116 women and 68 men).

Baseline assessment was extensive, involving pelvic CT and included hip pain specific questions from the AGES-Reykjavik questionnaire (which includes health history, lifestyle practices, a medication survey, and a food history including early-life diet and social aspects of daily life) as demonstrated by *Table 3.1*. At the baseline visit, height and weight were measured.

Variable	Description
HEALHIPA	Have you ever had pain in or around either hip joint, including the buttock, groin or either side of the upper thigh, lasting at least one month?
HEALHP12	In the past 12 months, have you had pain in or around either hip joint, including the buttock, groin or either side of the upper thigh, lasting at least one month?

Table 3.1: Hip Pain Questions

3.1.4 CT Image Acquisition

CT images of hips were acquired in the supine position using a standard clinical CT system (Somatom Sensation, Siemens Medical Systems, Germany). Scans were acquired using a standardised protocol and encompassed the proximal femur from a level 1cm above the acetabular margin to a level at least 3mm below the lesser trochanter. Scan settings: 120kVp, 140mAs, 1mm slice thickness, pitch=1, xy pixel dimension of 0.977mm and 512x512 matrix in spiral reconstruction mode using standard kernel with a 50cm reconstruction field of view.

An experienced musculoskeletal radiologist (Thomas D. Turmezei (TDT)) blindly scored the osteophyte load in 3D using the multiplanar reformatted images of the CT scans, using published methods.[1] Multiplanar reformatting was used to make a mean intensity projection slab aligned symmetrically in the axial plane to a true sagittal plane through the pubic symphysis, with coronal coverage of the anterior and posterior hip joint margins (*Table 3.2*).

Osteophyte score (excluding the reaction area & fovea)		
0	0 – 4 (sum of osteophyte sector scores from severity mapping)*	
1	5 – 9	
2	10 – 19	
3	>20	
Subchondral cyst score (excluding the neck or pit area)		
0	Everything but grade 1 (grade from severity mapping)*	
1	Any grade 3	
JSW score (number of sectors with score 3, JSW <1.5 mm)		
0	0 – 1 sector (derived from severity mapping)*	
1	2 – 3 sectors	
2	4 – 5 sectors	
3	6 – 7 sectors	
CT composite score**	CT grade	Verbal interpretation of CT grade
0 – 2	None (0)	No radiological osteoarthritis
3 – 4	Developing (1)	Developing radiological osteoarthritis
5 – 7	Established (2)	Established features of typical radiological osteoarthritis

*using the severity mapping of the proximal femur method; **CT composite score (0 – 7) obtained by summing osteophyte, subchondral cyst and JSW contingents.

Table 3.2: Interpretation of CT feature severity mapping score-sheets described in Turmezei et al. 2014, used to generate individual feature scores for CT composite score. CT composite score itemised into three separate CT grades

This resulted in a slab thickness in coronal depth that could be reviewed in the coronal plane as an AP pelvic radiograph, see *Figure 3.2*.



Figure 3.2: Coronal Mean Intensity Projection Slab (Usually 6–8cm In Depth) Showing The DRR Used For Minimum JSW Measurement And K&L Grading

The same radiologist blindly graded AP mean intensity projection reformatted images, DRR of the CT data to score osteoarthritis in each hip according to the Kellgren and Lawrence (K&L) score criteria, see (*Table 2.2*).

A magnification of up to 200%, see *Figure 3.3*, and a digital caliper tool was used to measure the minimal superior joint space width (mJSW) in a PACS viewer (OsiriX DICOM viewer software (©Pixmeo Sarl; v.3.9.3 32-bit, <http://www.pixmeo.com>)).

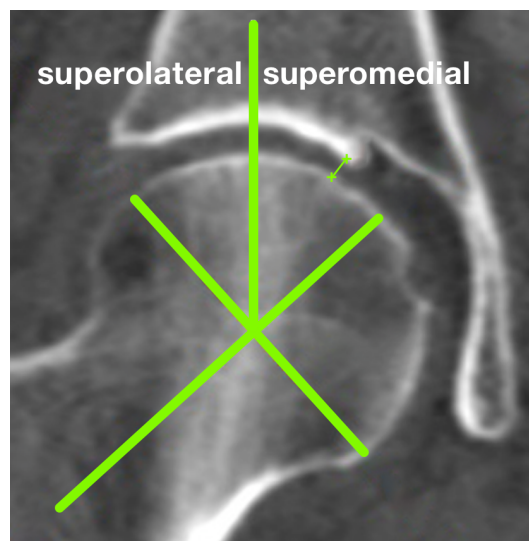


Figure 3.3: Representative image (in this case a coronal single slice) to demonstrate the location of mJSW measurement; the narrowest point by eye (to direct digital caliper placement). Note all mJSW measurements in the study were taken from a single radiograph

The weighted kappa statistics[1] of previous studies showed “almost perfect” intra-observer K&L grading for TDT (0.84 95% CI 0.57-1.00) but only “substantial” inter-observer reliability (0.63 95% CI 0.37-1.00), hence choosing a single radiologist in the present study.

“Cohen’s kappa statistic takes into account any disagreement there may be between two raters, but not the degree of their disagreement. Weighted kappa statistic is used to calculate using a predefined table of weights which measure the degree of disagreement between any two raters, the higher the disagreement the higher their weight. A table of weights should be a symmetric matrix with zeros in the main diagonal (i.e. where there is agreement between the two judges) and positive values off the main diagonal. The farther apart are the judgements the higher the weights assigned.”[295]

3.1.5 Methods Of Computational Analysis

Computational anatomy is a set of imaging analysis techniques that model anatomical structures in radiologically acquired images as curves, surfaces, maps, and volumes by combining them across subjects to create statistical feature maps.[296] When the statistical features are collected, they can be spatially analysed to detect subtle changes associated with prognosis, progression or treatment of conditions making it possible to visualise group differences or longitudinal changes as statistical maps.[297]

Computational analysis of image data acquired by CT is important in the assessment of osteoarthritis.[292] As mentioned[251, 252, 298] in 2011 a distinctive technique was developed to estimate and map cortical thickness, mass and density of a proximal femur known simply as CBM, it analyses CT data at multiple surface normal points. The technique works by estimating a standardised CT attenuation value of cortical bone.[251, 252] Further computational analysis techniques recently developed alongside engineers include statistical deformation modelling (SDM),[299] statistical parametric mapping (SPM),[300, 301] and Finite Element Modelling (FEM).[302] All of these techniques have the potential to determine thickness and biomechanics in osteoarthritis pathogenesis, therefore I selected these techniques to analyse the AGES data from Iceland. The CBM technique developed at the University of Cambridge, use clinical CT, with results validated (using cadaveric femurs) against data from HR-QCT acquired at a resolution of 82 microns per pixel. This technique has been noted to estimate individual cortical thickness measurements even in the clinically relevant sub-millimetre range. As long as there is an appropriate population study of indi-

viduals, as is the case with data from both the AGES and Mindways studies, SPM can be used to visualise and, more importantly, quantify the magnitude and statistical significance of differences.[251] The technique can also be used to estimate the cortical bone mineral density (CBMD),[252] response to treatment with teriparatide[253] and denosumab,[303] and has previously been applied to an investigation of patients who have fallen and fractured their hip. In that study the technique showed significant regions of cortical bone thinning in the hip that match fracture type.[254] The work conducted by[251] suggests that the true cortical thickness t_r is calculated by *Equation 3.1*; where t_m is the measured in-plane thickness, x_1 is the trabecular bone, x_2 is the cortical bone and a is the surface orientation angle.

$$t_r = t_m \cos a = (x_1 - x_2) \cos a \quad (3.1)$$

This equation allowed Treece et al. to begin calculations of the CBM by plotting CT value (HU) against distance (mm) to produce graphs, see *Figure 3.4*. Treece et al. explained that the CT value along a line passing through the cortex, see *Figure 3.4*, is simulated by blurring what is known as a “piece-wise constant density function” (with CT values of -1000, 1750 and 0) with a Gaussian kernel of standard deviation (SD) of 1mm.[251] The solid lines show the underlying and blurred CT values, the dotted lines show a threshold of 600, and the dashed lines show values half way between the appropriate CT baseline and the blurred peak (50% relative threshold).

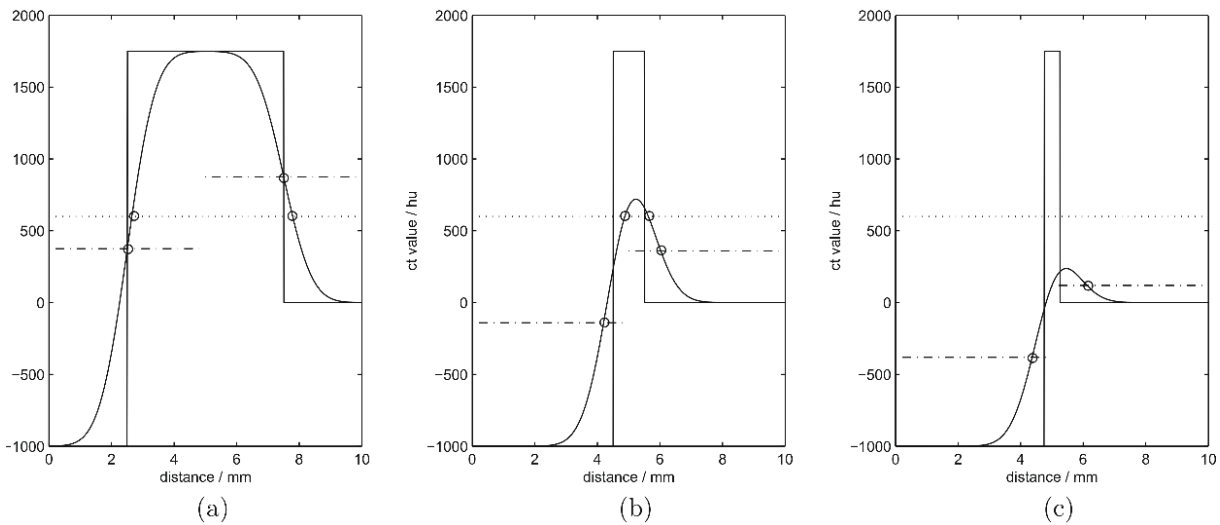


Figure 3.4: A Simulation Of The Cortical Imaging Process

Used From Figure 2[251]

If we analyse *Figure 3.4* further, the cortex in *Figure 3.4a*, is sufficiently wide for thresholding and the 50% relative threshold methods to work correctly. The threshold in *Figure 3.4b*, still gives approximately the correct thickness, but the 50% relative threshold method overestimates. No values exceed the threshold in *Figure 3.4c*, and the 50% relative threshold method now reports the width of the point spread function rather than that of the cortex.

In this Treece et al. presented a novel method for the estimation of cortical thickness using CT data. In the cadaveric experiments they conducted using the MDCT ($589\mu\text{m}/\text{pixel}$ resolution) method, which was able to produce unbiased estimates with an accuracy of 0.3mm. Unlike previous computational estimations, this method is highly automated and produces, on average, 17,000 independent thickness estimates over the proximal femur surface,[251] Which can be displayed as colours painted onto the 3D rendered surface with an appropriate scale, this can be seen in *Figure 3.5*.

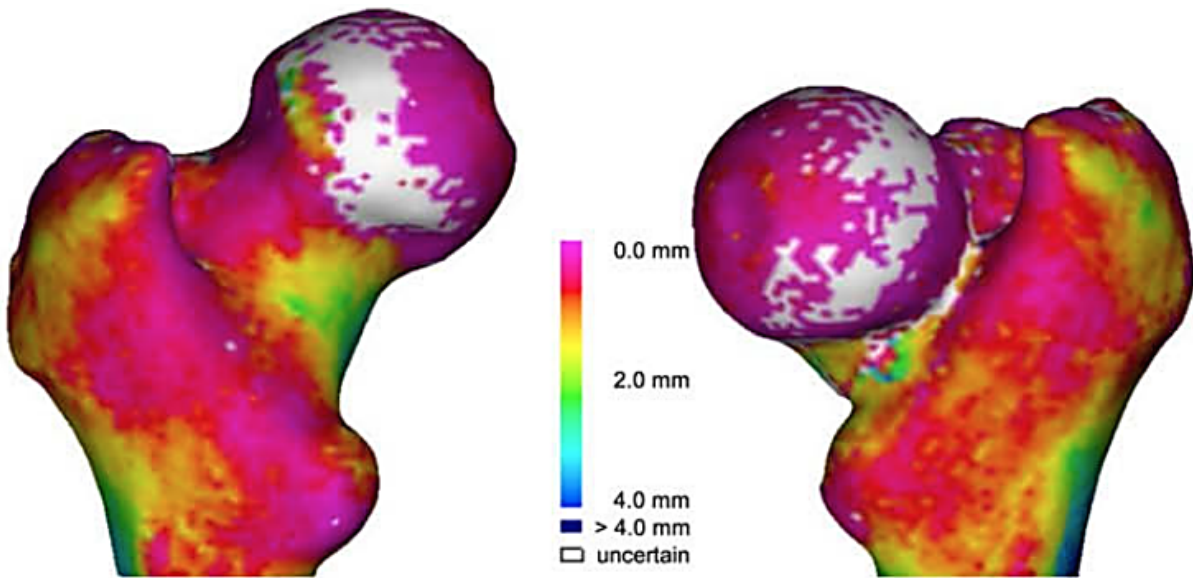


Figure 3.5: Cortical Thickness Estimation Colour Map On A 3D Surface

Used From Figure 14[251]

I selected this fully developed technique for both the AGES and Mindways study data sets, as it was the most up-to-date and efficient method known. The process can be summarised into nine basic stages represented by *Figure 3.6* and *Table 3.3*.

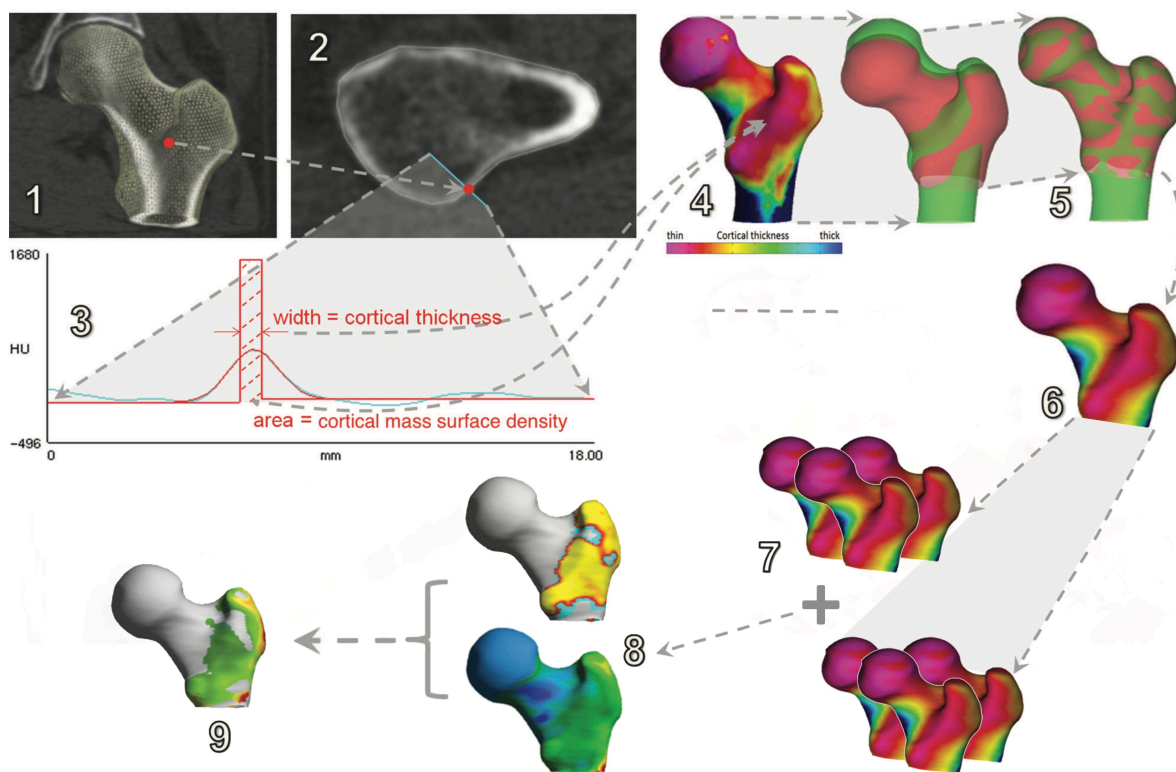


Figure 3.6: The Nine Stages Of Cortical Thickness Analysis

Image Adapted From Figure 2[304]

Stage	Process
1	Measurements are performed at every vertex in an approximate segmentation of a femur.
2	At each vertex, the CT data is sampled on a line passing through the cortex.
3	A model-based fit is used to estimate the cortical thickness, allowing for image blur.
4	The thickness is mapped back to the 3D surface as a colour (here blue is thick, pink is thin).
5	An average femur known as a canonical (red) is deformed to match the current femur (green).
6	Thickness estimates are transferred to the average femoral surface and a smoothing algorithm is applied.
7	This process is repeated for all subjects, producing subject-specific thickness estimates all mapped to the same average surface.
8	The data is analysed using statistical parametric mapping to obtain mean thickness differences between groups and also the significance of these differences.
9	One femur can model multiple differences between groups.

Table 3.3: Summary Of The Nine Stages For A Typical CBM Process

3.1.6 3D Cortical Bone Mapping

CBM is a technique[251, 252, 298] that estimates the cortical thickness (CTh) at thousands of locations distributed over the proximal femoral surface using the software tool *Stradwin* (<http://mi.eng.cam.ac.uk/~rwp/stradwin/>). The CBM technique generates a segmentation of the proximal femur represented by a triangular mesh of vertices. The CT data is sampled, and a model that accounts for the imaging blur is fitted to the data minimising the differences between the blurred model and the data. This is repeated at all vertices of the surface mesh, and the CTh can be visualised as a colour map on the femoral surface. The CBM technique, for the AGES study in particular, see *Figure 3.7*, is effective in ordinary clinical CT data-sets like these (thickness accuracy to 0.3mm with a mean \pm SD error of 0.01 ± 0.58 mm).[251]

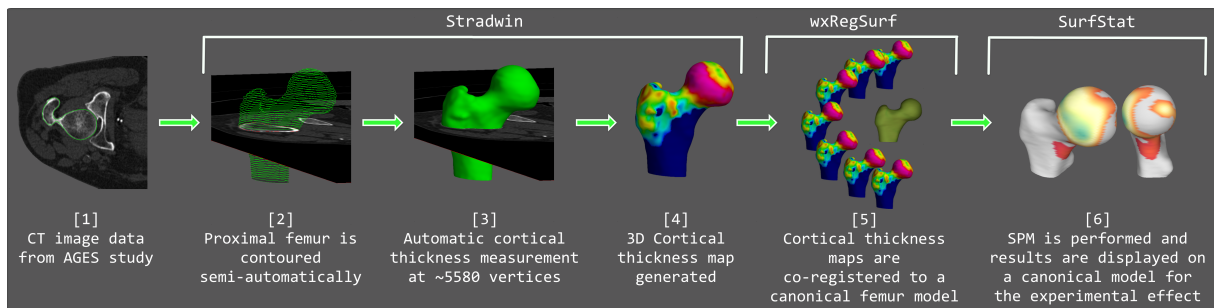


Figure 3.7: CBM Schema Demonstrating Pathway And Methodology

To allow for a population-based analysis of the cortical changes, a point correspondence has to be found between the surface maps of all femurs. A canonical proximal femur mesh is deformably registered to achieve this. After registration, the closest point on an individual subject mesh is found for each vertex in the canonical model, and the corresponding cortical measurement is copied onto the canonical shape. This ensures that for each new femur, the measurements can be related to the measurements on corresponding locations of all other femurs. The location and magnitude of patches of CTh associated with future THR can then be highlighted using SPM. To calibrate CT Hounsfield units to equivalent bone mineral concentration for this study, all subjects lay on a calibration phantom (Image Analysis, Columbia, KY, USA) containing four calibration cells for equivalent bone mineral, adipose tissue and water concentrations. If CBMD or endocortical trabecular density (ECTD) are required, an alternative, equally valid approach would be to calibrate the scanner once using a phantom set (known as “asynchronous QCT”), a phantom would no longer be needed.

3.1.7 Statistical Parametric Mapping

Hips differ from one another in shape and size; therefore, I needed to co-register all of the subjects onto a single “average” or canonical femur. The use of shape, modes in the general linear model (GLM), ensures that thicknesses are compared without the shape interfering (see *Appendix B*). An existing canonical proximal right femur mesh was deformably registered onto all surface meshes using a freely available in-house program called *wxReg-Surf* (<http://mi.eng.cam.ac.uk/~ahg/wxRegSurf/>). Each proximal femur was spatially re-aligned with a canonical right femur using locally affine deformation as calculated by an iterative closest-point registration algorithm.[299] For the left femur, the canonical mesh was mirrored to allow for the correct correspondences. After registration, for each vertex in the canonical model, the closest point on the target mesh was found, and the corresponding cortical measurement was copied onto the canonical mesh, meaning there was correspondence of measurement locations for all femurs. By examining corresponding points between THR cases and controls, I could map, visualise and statistically test the differences in cortical thickness over the whole surface of the proximal femur.[305] Corresponding measurement locations for each subjects lends itself to statistical testing in 3D using SPM. The data was smoothed over the surface during this process. SPM displays differences and their significance visually with a colour map on the canonical femur to show specific statistically significant regions of interest (ROI).

SPM was developed to compare data at multiple points in space and locate various regions of statistical variations with its earliest applications in neuroimaging of the brain. Statistical analyses on the femoral surface maps were performed using the SurfStat software package in *Matlab* R2016b (MathsWork, Inc., 1984-2016). In my case, the SPM technique has been adapted to perform statistical analysis of univariate and multivariate femoral surface data using linear fixed effect models and incorporating random field theory.[306] SPM involves fitting a GLM to account for variability in cortical thickness in terms of experimental and confounding effects (see *Appendix C*). The GLM allowed for variables: group (case/control), age, sex, weight, height, size (shape mode 0), neck length (SM1), neck shaft angle (SM2) and the remaining three non-rigid shape modes (SM) (shape modes 3-5).

$$CThGLM = 1 + group + age + sex + weight + height + SM0 + SM1 + SM2 + SM3 + SM4 + SM5$$

Standard two-tailed T-testing across the cohort gave p-values at each measurement location that were uncorrected for multiple comparisons. However, as essential for SPM, random field theory delivered p-values corrected for these multiple comparisons, thereby controlling for false positive results (type I errors).[307, 308] Both, the relative difference and significance, are presented simultaneously in my results, since those differences, that were statistically significant, are retained, and the remainder greyed out on the surface maps, see *Figure 4.1*. The primary outcome measure consists of the areas where cortical thickness differs between participants going on to THR and those who don't. To test the association between cortical thickness differences and clinical outcome (THR), all measurement points that are statistically significantly thicker (or less likely thinner) between groups are required. All surface locations where difference between groups occurs are averaged, to make a geographical "patch". An average thickness is calculated within the "patch" for each individual.

3.1.8 Statistical Methods

All statistical analyses were conducted using *Matlab*, *JMP* (v13.0 SAS Institute Inc., Cary, NC,1989-2007) or *Stata* Statistical Software (v14.2 StataCorp, TX, 2015). The baseline diagnostic/predictive measures tested were hip pain (positive answer to AGES codes HEALHIP12 question, see *Table 3.1*), osteoarthritis grade (by 2D K&L manual scoring), mJSW and 3D CTh in the patch. Structural measures were used in logistic regression to determine the OR for THR expressed per one SD increasing grade of K&L or decreasing mJSW or increase in CTh with adjustment for age, sex, height, baseline pain, femur shape, and following leave-one-out cross-validation (using *Matlab*). The area under the curve (AUC) was used to assess the performance of the model, with relevant 95% CIs. *JMP* was used to derive appropriate cut off values from Receiver Operating Characteristic (ROC) curves by minimising the Euclidian distances, "ROC and pAUC".[309] Also, within *JMP*, nominal logistic fit methods were used to examine the relationships between the various grades or increasing structural/imaging evidence of osteoarthritis and hip pain. Contingency analysis and the Clinical Utility index[310] was used to estimate the performance of diagnostic cut offs in regard to imaging utility in individuals presenting with baseline pain (a typical clinical pathway, "IVD performance v.12.0"[311] *JMP* Add-In). Associations were sought between HEALHIP12 (irrespective of THR status) and baseline hip structure. Performance of the various logistic regression models, including imaging performance with and without hip pain, was compared in STATA using the *roccomp* command and chi-square analysis.

3.2 Methods Of The 3D Printing Study

3.2.1 3D Printing Study Hypothesis

Hypothesis 3: The 3D printed model of the SPM osteoarthritis ROI result will help with the understanding of OA disease features.

3.2.2 Background

Safe, non-invasive and detailed imaging deep of an individuals' body to look at the bones inside remains a challenge in modern biomedical imaging. Interpreting radiographic images, if one does not come from a technical radiological background, may be difficult. Trying to look for bone disease features in an individual is also challenging. Studying how this individuals' disease features compare to others in a population is even more of a challenge.

X-ray imaging gave us the ability to non-invasively view the skeleton, but this converted the 3D human body into a flat 2D image. Revolutionary advances in imaging technology with the development of CT, MRI, MDCT etc imaging (see Chapter 2) not only gave us the ability to see inside the human body in greater detail, but it once again gave us the possibility of rendering and visualising it in virtual 3D. This transformation from 2D to 3D was hailed as the next big step in medical imaging when it was introduced over the last few decades. A typical detailed procedure to study bone uses CT images. This means that 100-300 sliced 2D images are taken with a particular size/thickness and space covering a particular region (for example, 300 images at 1mm intervals). A virtual 3D model can be built up from these layers of 2D images. Although the new imaging technologies helped radiologists, clinicians and patients better visualise/interpret the body, the human brain naturally processes physical objects to give depth information, and thus "Virtual 3D" images are still just 2D images with a simulation of the third dimension of depth.

A simulated, virtual image on a screen is not equivalent to the visual experience of a physical 3D object. Therefore 3D printing of anatomic models is the next advancement in medical imaging.[312–315] Since the late 1980's, additive manufacturing, rapid prototyping or 3D printing (as it is now commonly known) has been expanding and gaining popularity.[316] Traditionally it was not used in medical applications, but with the development of newer, faster and more accurate technologies, it has entered the medical field. Medical applications for 3D printing are rapidly expanding and are predicted to revolutionise health care.[313]

Uses of 3D printing in medicine is generally divided into two viewpoints: actual and potential. Actual uses of 3D printing include anatomical model fabrication, tailored prosthetics and implants. Whereas potential uses of 3D printing may include tissue and organ fabrication, pharmaceutical drug delivery and drug dosage.[317] The cost of a 3D printed model is a fraction of what it would normally cost to order custom built models, with a quicker turn-around time from order to delivery.[318]

3D printed models add the concept of “touch to comprehend”[319, 320] which combines natural biocular vision with multisensory inputs of touch. In numerous studies, surveys that surgeons completed about the utility of 3D models given to them before surgery concluded that in all cases, the surgeons found the models to be helpful.[321–323] So I became interested in 3D printing the femoral structure generated which displayed “average” or archetypal osteoarthritis features, see *Figure 4.1*, not only at full scale while representing disease features in printed colour on this 3D printed model.

3.2.3 3D Printing Study

I realised that my results could be visualised on a flat 2D computer screen with a virtual 3D appearance but I felt that due to the complex structure of the anatomy of the femoral head and acetabular bone interaction I couldn’t reliably visualise it virtually. In this study I wanted to have a hands-on visualisation of how cortical thickening in osteoarthritis related to functional anatomy. I utilised an anatomical hip joint model with attached labrum and prosthetic ligaments. I then needed to visualise typical hip movements in the canonical hip, particularly I was interested in the correspondence between the statistical significant thickness printed on in colour and the 3D joint structure as a whole. So I decided to create a 3D printed model of the SPM surfstat output, in order to better understand and communicate my findings from the AGES study in a more tangible, easy-to-understand format.

3.2.4 Principles Of 3D Printing

3D printing in radiology is the process of fabricating or “printing” an object that is depicted on Digital Imaging and Communications in Medicine (DICOM) images acquired from a typical radiological scan. In general, 3D printers do not yet accept DICOM images as they are not yet able to generate the exact object that needs to be printed. As described in the CBM process, see *Figure 3.7*, the 2D DICOM images are imported into *Stradwin*, and

segmentation of the anatomy is performed to generate a 3D virtual computer model of the anatomy of interest. After the SPM analysis script is run in *Matlab*, a new 3D image is generated with ROIs (this was step 6). The file generated is still not readable by a 3D printer because it needs an Standard Tessellation Language (STL) or a Virtual Reality Modeling Language (VMRL), also known as a .wrl file (this is step 7 of the post CBM pathway). STL files cannot be used to print colour 3D models[324], so I decided to write a *Matlab* script (see *Appendix D*) to export my SPM surfstat generated image into a .wrl file that could be easily read by the 3DPrint (see *Figure 3.8*).

A .wrl file is a plain text file that includes data specifying details, see *Figure 3.8*, such as XYZ coordinates, colour per vertex, and coordinate indexes for a 3D model.

<pre>#VRML V2.0 utf8 Transform { children [Shape { appearance Appearance { material Material { ambientIntensity 0.2 specularColor 0.1 0.1 0.1 emissiveColor 0 0 0 shininess 0.2 transparency 0.200 } } geometry IndexedFaceSet { coord Coordinate { point [27.20135 -0.50890 39.57809, 25.18938 0.68712 39.67686, 27.23356 1.53528 39.62533, 25.23662 2.75277 39.56950, 25.09919 -3.95309 39.02195, 22.73078 -2.51228 39.07778, 27.45472 -2.68836 39.21735, 20.73383 -0.77945 38.86735, 25.02619 -1.57608 39.45355, 29.60841 -0.79233 39.17870, 22.89611 0.29417 39.36766, 28.54553 0.47239 39.53085, 31.22529 0.44878 38.89956, 20.80684 1.50737 38.91030, 23.93538 1.81443 39.59527, 29.77375 1.97547 39.20018, 22.91329 3.17578 39.21950, 27.45258 3.77916 39.35907,] } }</pre>	<pre>colorPerVertex TRUE color Color { color [0.992156863 0.71372549 0.396078431 , 0.996078431 0.756862745 0.419607843 , 0.988235294 0.631372549 0.360784314 , 0.992156863 0.682352941 0.384313725 , 0.996078431 0.874509804 0.549019608 , 0.996078431 0.989803922 0.619607843 , 0.996078431 0.764705882 0.423529412 , 0.996078431 0.933333333 0.662745098 , 0.996078431 0.823529412 0.474509804 , 0.988235294 0.631372549 0.360784314 , 0.996078431 0.854901961 0.517647059 , 0.988235294 0.623529412 0.352941176 , 0.980392157 0.549019608 0.317647059 , 0.996078431 0.894117647 0.584313725 , 0.996078431 0.788235294 0.439215686 , 0.976470588 0.537254902 0.309803922 , 0.996078431 0.788235294 0.439215686 , 0.980392157 0.556862745 0.321568627 , 0.984313725 0.611764706 0.349019608 , 0.964705882 0.466666667 0.278431373 , 0.968627451 0.474509804 0.282352941 , 1.000000000 0.988235294 0.745098039 , 0.996078431 0.862745098 0.529411765 , 1.000000000 0.992156863 0.749019608 , 0.996078431 0.917647059 0.631372549 , 0.996078431 0.737254902 0.407843137 , 1.000000000 0.996078431 0.749019608 ,]</pre>	<pre>] } coordIndex [6, 8, 4, -1, 4, 8, 5, -1, 0, 8, 6, -1, 1, 8, 0, -1, 5, 8, 10, -1, 10, 8, 1, -1, 0, 6, 9, -1, 0, 9, 11, -1, 2, 0, 11, -1, 1, 0, 2, -1, 10, 1, 14, -1, 3, 1, 2, -1, 14, 1, 3, -1, 15, 11, 9, -1, 2, 11, 15, -1, 16, 10, 14, -1, 10, 16, 13, -1, 16, 14, 3, -1, 17, 2, 15, -1, 2, 17, 3, -1, 18, 3, 17, -1, 18, 16, 3, -1, 19, 17, 15, -1, 17, 19, 20, -1, 17, 20, 18, -1, 21, 24, 27, -1, 21, 27, 23, -1,]</pre>
(a) XYZ Coordinates	(b) Colour Per Vertex	(c) Coordinate Index

Figure 3.8: 3D Image .wrl Script Output Generated

The .wrl file is then imported (as a 3D interactive image) into the 3D printer software (3DPrint) to be checked and prepared for printing as seen on *Figure 3.9*

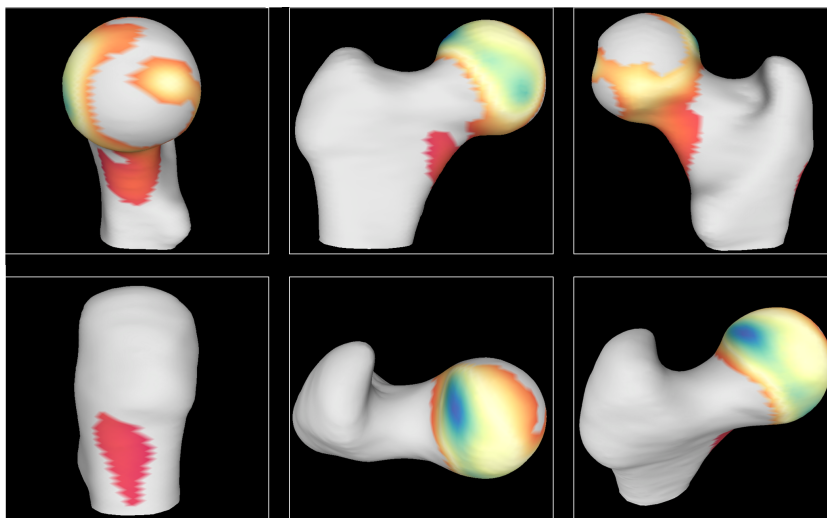


Figure 3.9: Output of .wrl File Export From *Matlab* Script For 3D Printing

3.2.5 The 3D Printing Workflow

The workflow from image acquisition to 3D printed object (specifically for my 3D model) is shown in *Figure 3.10*. Several important methodological steps, necessary supplies, temperatures, as well as times, are shown in this workflow.

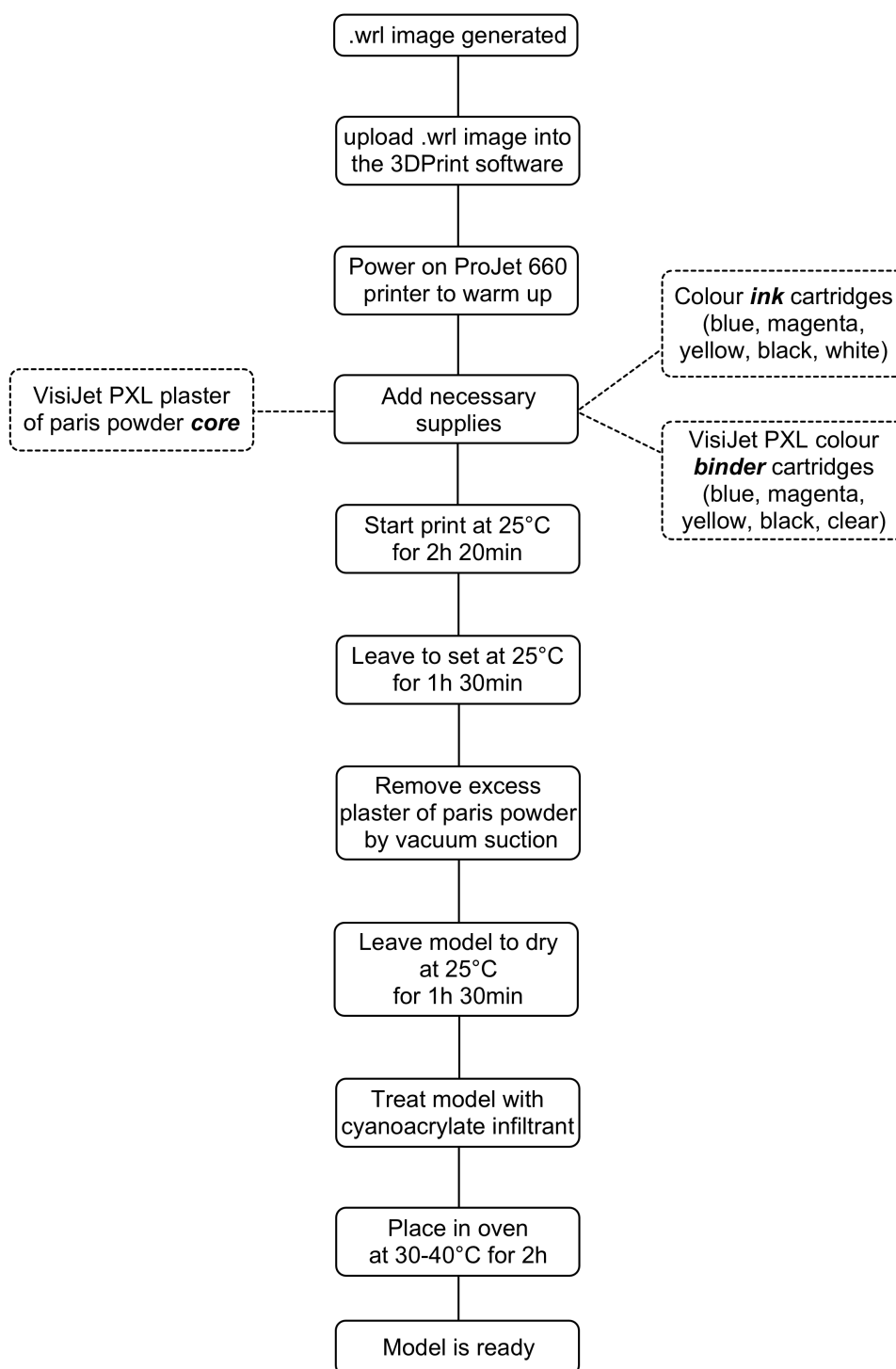


Figure 3.10: 3D Printing Process Flowchart Representing The Work Plan Form Imaging Data To 3D Printer Object

3.2.6 The 3D Printer Hardware



Figure 3.11: ProJet 600Pro 3D Printer

Although there are many different types of 3D printers, I was limited to what the Addenbrooke's hospital Media Studio had which were either the Binder Jetting (colourful Plaster of Paris models from fine powder) and Material Extrusion (single colour plastic extrusion) type of 3D printers. Luckily, Binder Jetting 3D printing is exactly I needed because it is the most accurate and easiest 3D printing process to produces truly multi-coloured and durable printed models.

The 3D printer used for the printing process is the ProJet 600Pro (late 2015 version) manufactured by 3D Systems Inc., see *Figure 3.11*. The 600Pro is known as a “Binding Jetting” printer, otherwise known as a powder ink jet 3D printer. It uses a print head to jet a liquid binding agent onto a bed of fine powder. The printer incorporates professional 4-channel cyan, magenta, yellow, and key (black) (CMYK) full-colour 3D printing capability for realistically accurate and consistent colour model printing. The printer is fast and produces high resolution 3D prints. It also uses eco-friendly, non-hazardous materials with zero liquid waste. The printing process begins at 25°C and takes 2 hours and 20 minutes to complete. The binding agent, which in my case needs to be in colour, selectively bonds the powder wherever the nozzle deposits it. After a layer is completed, the nozzle moves up and more powder is deposited for the new layer on top. This ensures that the model grows (from bottom up) on the metal surface bed.

3.2.7 3D Printing Supplies

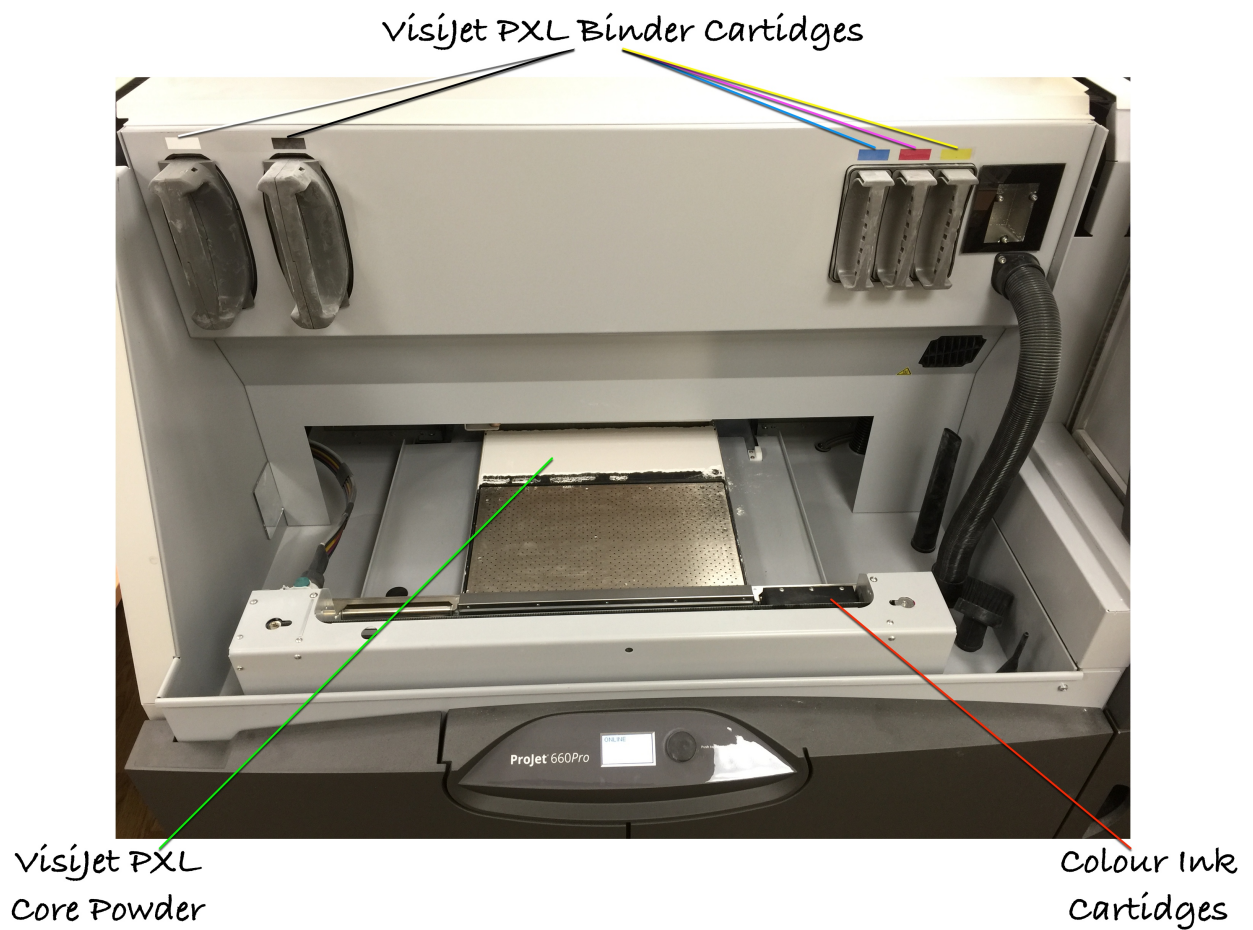


Figure 3.12: ProJet Supplies Arrangement

In order to produce a 3D printed model there must be an adequate supply of VisiJet PXL Binder cartridges, VisiJet PXL Core powder and Ink cartridges, see *Figure 3.12*.

The VisiJet PXL Binder cartridges, see *Figure 3.13*, are coloured liquids (blue, magenta, yellow, black, clear) that are dispensed through a HP11 print head, see *Figure 3.14b*, and applied to the VisiJet PXL Core material. The Binder is applied to the edges of the model with a higher saturation in order to create a stronger exterior part of the model. The interior areas of the model are printed with low Binder saturation. The Binder is applied layer by layer from bottom to top as the model grows.

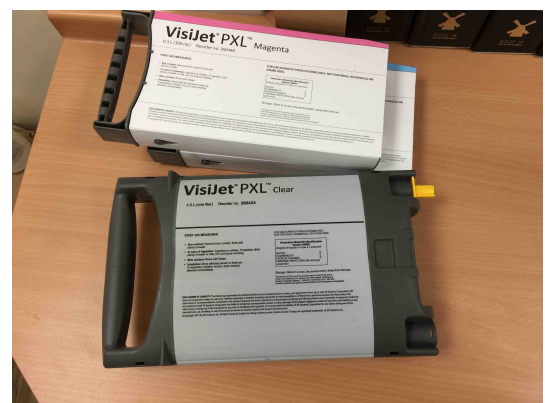
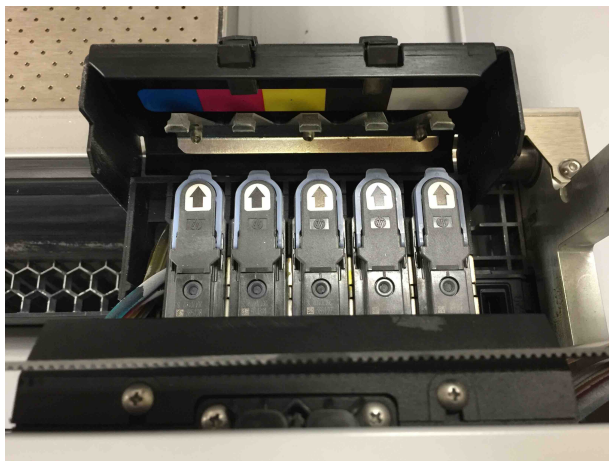


Figure 3.13: VisiJet PXL Binder

There are five HP11 print cartridge heads and they are arranged as seen in *Figure 3.14a*. These print heads are responsible for printing the pattern of the model by gently squirting drops of the PXL Binder, see *Figure 3.13*, onto the PXL Core material, see *Figure 3.15*, in order to form a structure.



(a) Ink Cartridge Arrangement



(b) Individual Ink Cartridge

Figure 3.14: 3D Printer Ink Cartridges

The VisiJet PXL Core is a powder type material similar to plaster and is non-toxic, see *Figure 3.15*. It is what makes the model structure when a Binder liquid is added. Unlike with other 3D printing processes, support structures are not necessary because the model is supported by unbonded Core powder from all sides. Before the printing process can begin, a layer of Core material needs to be smoothly spread on the build bed. When the printing is finished, excess Core material around the model needs to be vacuumed (the Core material not used can be indefinitely re-used for the next print until there is no more Core material left). After the model has printed, it needs to be left to set at 25°C for 1 hour and 30 minutes. Then it can be removed from the printer and undergo cleaning, see *Figure 3.16*.

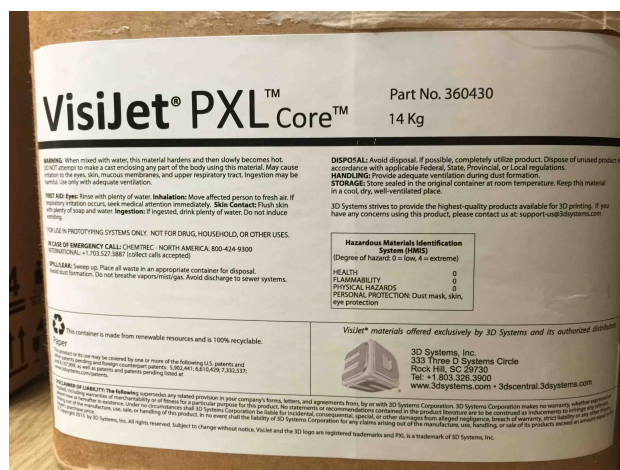
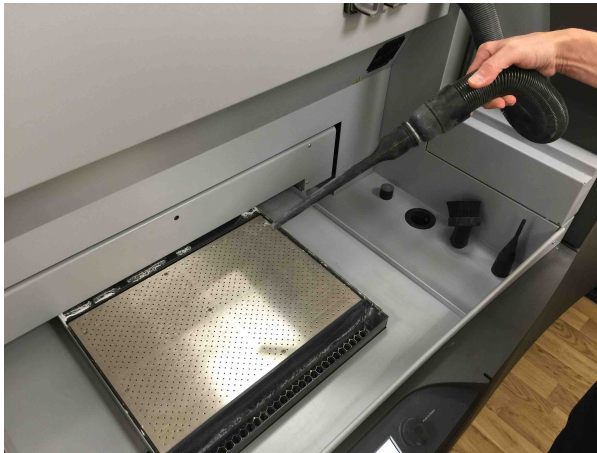


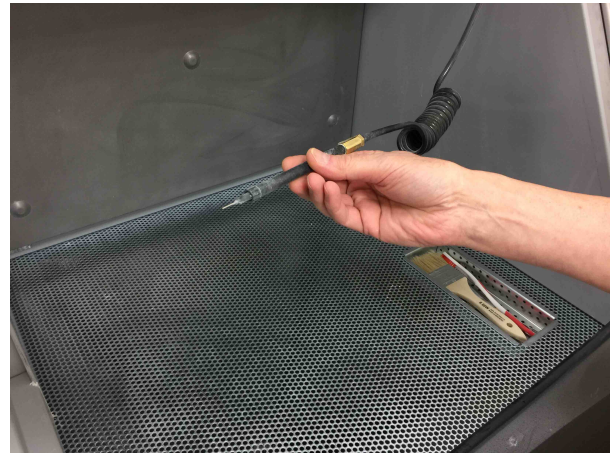
Figure 3.15: VisiJet PXL Core

3.2.8 3D Printed Object Cleaning

After the printing and drying process, the cleaning step involves vacuuming and blowing off any excess unbonded Core powder, see *Figure 3.16a*. When the majority of the excess core powder has been removed, the model is moved to the fine cleaning area which blows off remaining Core material using compressed air and various soft brushes, see *Figure 3.16b*. After the cleaning process, the model needs to be left to dry at 25°C for a further 1 hour and 30 minutes before it can undergo Cyanoacrylate infiltrant adhesive treatment.



(a) Model Cleaning Process



(b) Fine Cleaning Process

Figure 3.16: Post 3D Printing Model Cleaning Process

3.2.9 3D Printed Object Treatment

Because the plaster-like Core materials are generally fragile, even after several heat drying treatments, care must be taken when handling the printed model to minimise the likelihood of damage. This is where infiltrant treatment with Cyanoacrylate infiltrant solution, see *Figure 3.17*, is necessary as it gives the model additional strength and durability to make it safer to handle. The printed model is dipped into an open bath of Cyanoacrylate infiltrant until it is fully covered, then it is placed into an oven at 30–40°C for 2 hours to ensure that the glue has set properly.

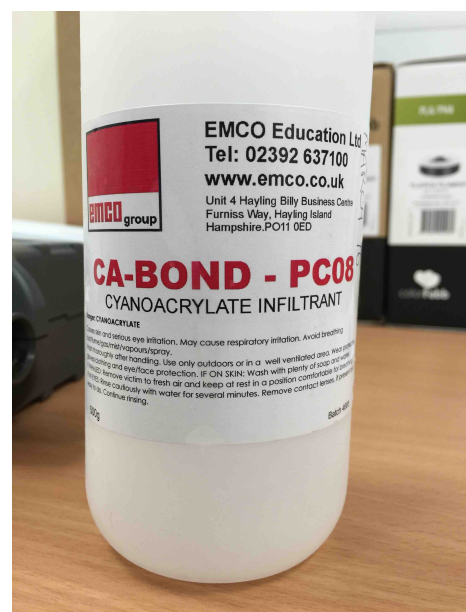


Figure 3.17: Cyanoacrylate Infiltrant

3.3 Methods Of The Mindways Ageing Study

3.3.1 Hypothesis of Mindways Ageing Study

Hypothesis 4: Distribution of cortical bone in the femoral head will become “osteoarthritic” with ageing which will manifest as regional “thickening”.

3.3.2 Background

Previous imaging studies have revealed decreases in proximal femoral bone strength and cortical bone thinning in older adults compared to younger adults.[325, 326] However, in osteoarthritis of the femoral head, cortical bone thickening is observed, paradoxically. Given the relatively strong association between age related bone changes and cortical bone structure, particularly in women, see *Section 1.6.3*, I set out to investigate if regional femoral cortical bone thickening was an inevitable consequence of ageing or only occurred in select osteoarthritis-prone individuals. I applied the CBM technique, see *Section 3.1.6*, and quantitatively examined in detail, how the femoral head bone cortex changes with age. Using data from a large cross-sectional cohort, I investigated standard imaging measures of cortical bone thickness. I hypothesised that the region of femoral head patch generated by CBM would generally thicken with age as part of an inevitable “wear” pattern affecting the overlying cartilage.

3.3.3 Study Population

The Mindways study (based on data collected by Mindways Software Inc. (Austin, TX, USA)) is a cross-sectional study that recruited 630 Caucasian women aged 19-97 years (mean 47 ± 17 SD) between 1998 and 2002 at 11 centres all across the USA, see *Figure 3.18*.

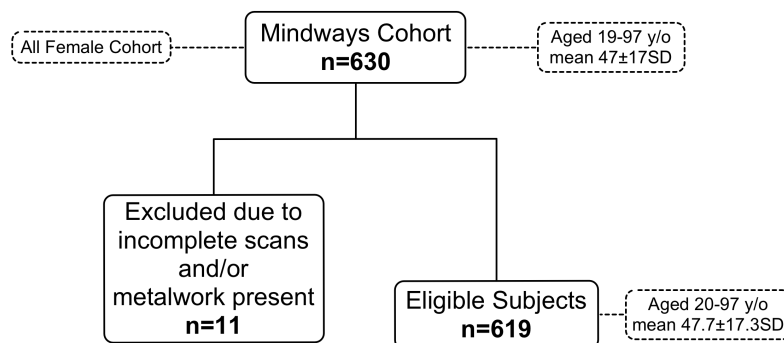


Figure 3.18: Schematic Representation Of Mindways Ageing Study Subjects Inclusion And Exclusion Criteria

The 11 recruitment centres included AD (Decatur, Indiana), BERG (San Luis Obispo, California), BH (Bar Harbor, Maine), CF (Cannon Falls, Minnesota), CU (Gold Beach, Oregon), FR (Los Angeles, California), MA (Rochester, Minnesota), MD (Owensboro, Kentucky), MN (Millinocket, Maine), RF (Skowhegan, Maine) and SCH (Schnectady, New York), see *Figure 3.19*.

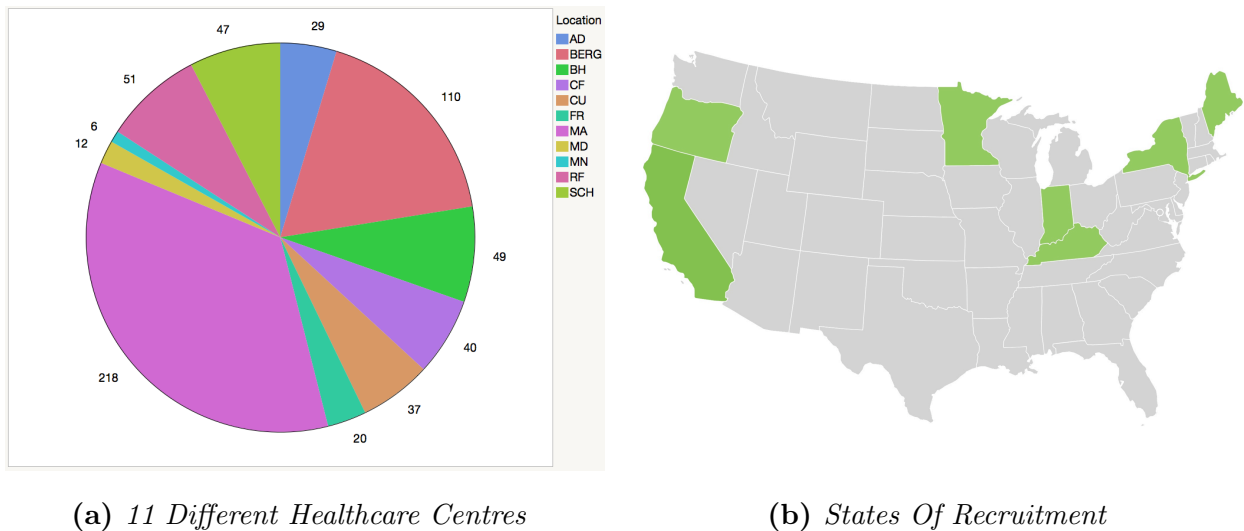


Figure 3.19: Locations Of Mindways Study Data

The cohort included women having bone mineral density (BMD) assessments as part of their standard clinical evaluation as well as some volunteers who desired an assessment. Clinical QCT data from the femoral head down to the lesser trochanter was obtained using the Mindways hydrogen dipotassium phosphate liquid calibration phantom (K_2HPO_4). The data was collected for FDA (510k) approval (K030330) and was subject to Investigational Review Board oversight. Of the 630, 11 subjects were excluded due to having incomplete scans (in some cases due to the presence of metalwork). The final study number of subjects was 619, aged 20-97 years (mean $47.7 \pm 17.3SD$) summarised in *Figure 3.20*.

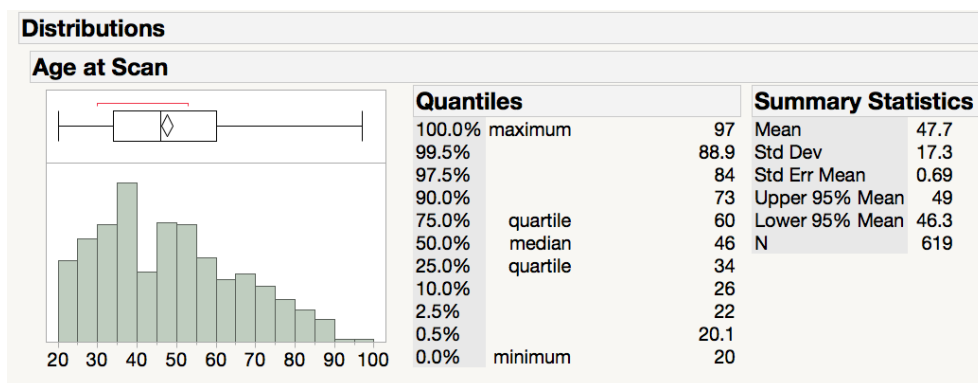


Figure 3.20: Age Distribution

3.3.4 Bone Measurements

Similar to the method of the CBM technique carried out for the AGES Study, see *Section 3.1.6*, cortical bone thickness measurements of each proximal femur were made using the *Stradwin* software package. Using this software, the contours of the bone surfaces are semi-automatically drawn on the QCT slices. These were then processed into a triangular surface mesh on which the cortical measurements are performed. Samples were taken in the QCT volume, perpendicular to the bone surface, resulting in a profile of the QCT values with an inherent smoothness. By fitting a blurred model of the cortex to the data samples, *Stradwin* was able to accurately estimate the cortical thickness (measured in mm).

3.3.5 Statistical Analysis

Using the CBM output file and the cortical thickness values for each subject that were available, I was able to plot and analyse (using *JMP* Statistical Software, see *Section 3.1.8*) how the cortical thickness average per vertex values as well as the mean cortical thickness in the ROI varied with age. This would demonstrate the relationship and significant cortical bone thickness changes with ageing.

I modelled the data using standard modelling (linear regression) but, because my data was non-linear, I decided to continue my analysis using quadratic modelling (quadratic regression) as the latter allows for different rates of change at different ages and the possibility of detecting the age at which the CBM measure is largest.

Chapter 4

Results

4.1 Results Of The AGES Study

Hypothesis 1: 2D imaging will have clinical utility in predicting hip replacement in those with hip pain.

Hypothesis 2: The 3D distribution of cortical bone thickness around the proximal femur will predict hip replacement in those with hip pain.

4.1.1 Predicting Total Hip Replacement

Patients were well matched at baseline, see *Table 4.1*. Approximately two thirds of the study participants were female. The average age of participants was 74 years (± 4.7 years). Cases underwent THR 35.8 months (± 23.7 months, range 1–96 months) after their baseline CT scan. The presence of hip pain was a poor to marginal predictor of THR (AUC 0.70, cross-validated 0.63). Only 45% (33/74) of patients destined for THR reported hip pain at the time of their CT scan. Of those 33 THR cases, the number of days until replacement was available for 30 people. As expected, those 30 with baseline pain underwent surgery earlier (average 28.9 months ± 25.2 months, $p=0.04$), then the 41 who developed symptoms later (THR at 40.8 months ± 21.4 months, $p=0.04$). Next, I assessed the additional discriminatory ability of different imaging outcomes for THR. Adding any radiological measurement to hip pain alone greatly enhanced the prediction of THR, see *Table 4.2*. Adding a simple distance measure (2D mJSW) improved discrimination from 0.70 AUC to 0.80 ($p=0.02$). mJSW was non-normally distributed with a positive skew in cases and controls, with zero values common in those destined for THR. As expected a wider hip joint space (mJSW) was protective against THR, and even on its own without considering pain status gave an

Baseline Data	Total Subjects (n=258)		Females (n=164)		Males (n=94)	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of subjects	184 (71%)	74 (29%)	116 (71%)	48 (29%)	68 (72%)	26 (28%)
Age ± SD (years)*	74.0 ± 4.7	74.0 ± 4.7	74.1 ± 5.0	73.6 ± 4.6	74.8 ± 4.6	74.8 ± 4.9
Height ± SD (m)*	1.68 ± 0.09	1.67 ± 0.09	1.62 ± 0.05	1.62 ± 0.06	1.77 ± 0.07	1.75 ± 0.06
Weight ± SD (kg)*	77.5 ± 13.6	78.1 ± 12.7	73.1 ± 12.8	76.5 ± 12.0	85.0 ± 11.6	80.9 ± 13.6
Hip pain in the past 12 months	19 (10%)	33 (45%)	15 (13%)	24 (50%)	4 (6%)	9 (35%)
Mean CTh in ROI ± SD (mm)	1.1 ± 0.1 [†]	1.3 ± 0.2 [†]	1.1 ± 0.1 [†]	1.3 ± 0.2 [†]	1.1 ± 0.1 [†]	1.4 ± 0.2 [†]
Median minJSW 2D IQR (mm)	2.3 (1.8, 2.8) [†]	1.1 (0.6, 1.9) [†]	2.0 (1.5, 2.6) [†]	1.1 (0.4, 1.8) [†]	2.6 (2.0, 3.0) [†]	1.6 (1.0, 2.6) [†]

K&L Score***	Total Hips Analysed** (n=458)		Females (n=291)		Males (n=167)	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of hips	368 (80%)	90 (20%)	232 (80%)	59 (20%)	136 (81%)	31 (19%)
Grade 0; no OA	279 (76%)	18 (20%)	170 (73%)	9 (15%)	109 (80%)	9 (29%)
Grade 1; doubtful OA	53 (14%)	13 (15%)	34 (15%)	8 (14%)	19 (14%)	5 (16%)
Grade 2; mild/minimal OA	26 (7%)	19 (21%)	20 (9%)	13 (22%)	6 (4%)	6 (19%)
Grade 3; moderate OA	10 (3%)	30 (33%)	8 (3%)	23 (39%)	2 (2%)	7 (23%)
Grade 4; severe OA	0 (0%)	10 (11%)	0 (0%)	6 (10%)	0 (0%)	4 (13%)

*Entire Dataset; **relevant hip (i.e. replaced) of randomly selected cohort; ***Kellgren and Lawrence (K&L) grade for Flattened 2D MPR view of CT data [†]p<0.0001;

Table 4.1: Baseline AGES Data

AUC of 0.79 (OR 0.26 per SD thicker, 95%CI 0.2, 0.4) increasing to 0.80 with baseline pain included, see *Table 4.2*. As K&L grades of the 2D radiograph increased, there was an exponentially increasing OR for THR. The model including K&L gave an AUC of 0.87 (OR 6.30 per incremental K&L grade, 95%CI 4.0, 10.0), unchanged by including baseline pain. K&L gave better discrimination than the more basic mJSW (0.87 vs 0.80 $p=0.0056$). Either manual K&L grade or 3D CTh were the best, and interchangeable single discriminators in those with hip pain (AUC 0.87 with K&L and 0.85 with CTh, $p=0.29$, see *Table 4.2*). However, 2D K&L grading and 3D CTh seem to provide different information, as manifest by excellent discrimination of THR from control seen in a model containing; pain, K&L grade and 3D CTh (AUC=0.90). Differences in baseline CTh between subjects who went on to have THR and matched controls are displayed as a statistical difference map with a colour scale for the magnitude of the relative differences (colour map, see *Figure 4.1*). Grey areas are regions where there was no statistical significance between THR patients and controls. Blue, yellow and orange areas demonstrate 35–70% thicker femoral head bone in the focal areas. The average CTh from within the multi-coloured ROI, see *Figure 4.1*, was used for further analysis, with values and SD, see *Table 4.1*.

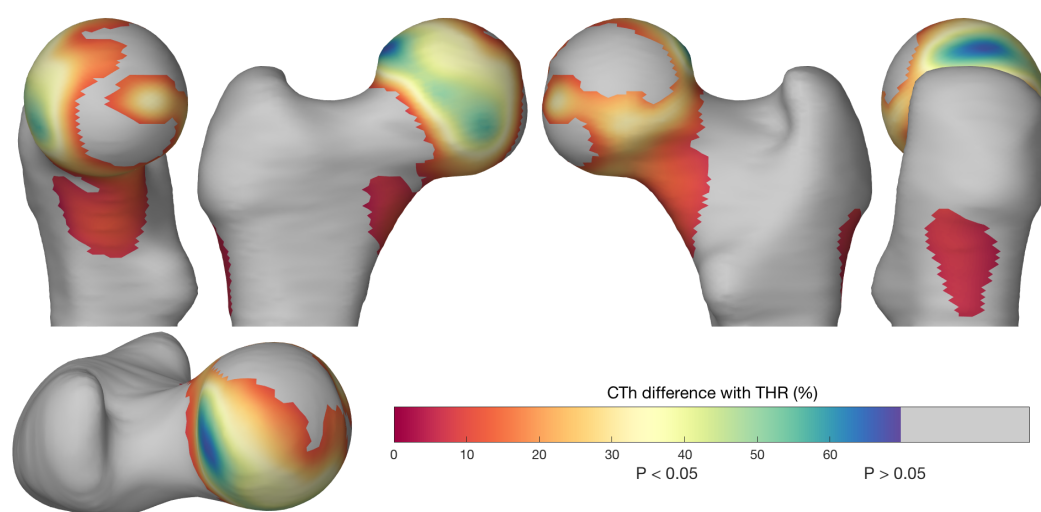


Figure 4.1: SPM generated cortical thickness image showing a statistically significant thickening circumferentially around the periarticular margin, with up to 70% thicker (green/blue) cortical bone at baseline in subjects who went on to have THR

The model containing average CTh from this ROI (alongside age, sex, height) predicted incident THR well (see *Table 4.2*), with an area under the receiver operating curve of 0.83 (OR 5 per SD thickening, 95%CI 3.2, 7.7). Adding baseline pain to the model increased AUC slightly to 0.85. 3D osteophyte load[1] accounted for 25% of the variance, see *Figure 4.2*,

in CTh within the ROI (CTh in ROI=1.2–0.01*Osteophyte load, $p<0.0001$, adj $R^2=0.25$). While osteophytes did not fully explain cortical thickening, THR prediction in ROC analysis was the same whether 3D osteophyte load or CTh was modelled (AUC 0.83). Thinning of the joint space was only weakly associated with cortical thickening in cases (not controls) explaining 6% of the variance in CTh (CTh in ROI=1.4–0.05*mJSW, $p=0.03$, adj $R^2=0.06$), see *Figure 4.3*.

Model	AUC (95%,CI)	AUC*	OR per SD (95% CI)	Hip pain only vs hip pain + imaging (χ^2)	prob> χ^2
hip pain only	0.70 (0.62–0.78)	0.63	2.21 (1.68–2.91)	-	-
Joint Space Width (mJSW)	0.79 (0.72–0.86)	0.77	0.26 (0.17–0.39)	-	-
<i>i</i> hip pain + mJSW	0.80 (0.73–0.87)	0.78	-	5.75	0.0164
OA Score (K&L)	0.87 (0.81–0.92)	0.85	6.30 (3.96–9.99)	-	-
<i>ii</i> hip pain + K&L	0.87 (0.82–0.93)	0.85	-	20.35	0.0000
Cortical Thickness (CTh)	0.83 (0.77–0.89)	0.81	5.00 (3.24–7.71)	-	-
<i>iii</i> hip pain + CTh	0.85 (0.79–0.91)	0.83	-	14.30	0.0002
hip pain + K&L + CTh	0.90 (0.85–0.95)	0.88	-	26.80	0.0000

ROC, Receiver operating characteristic; AUC, area under the curve; AUC*, cross validated area under the curve; OR, odds ratio per standard deviation (SD); CTh, cortical thickness; mJSW, minimum joint space width; K&L, Kellgren and Lawrence score; χ^2 =chi-square test; i vs ii, $\chi^2=9.25$, $p=0.0024$; i vs iii, $\chi^2=2.21$, $p=0.1375$; ii vs iii, $\chi^2=0.48$, $p=0.4881$.

Table 4.2: Predicting THR for OA within 3 years (± 2 yrs); using baseline hip pain alone versus adding imaging tests (comparison of area under the ROC curve of various models)

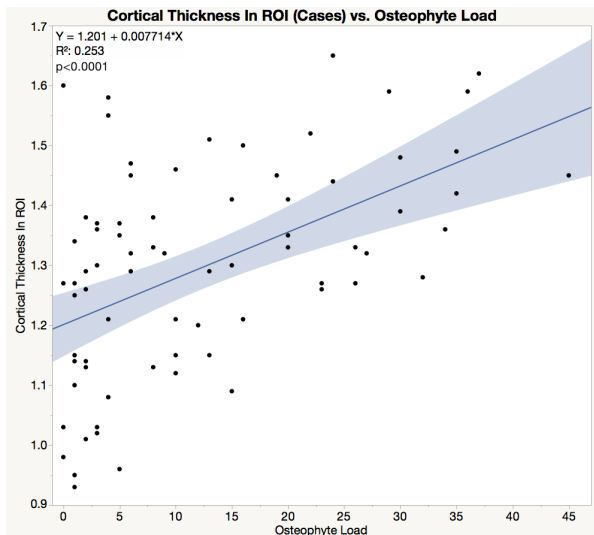


Figure 4.2: Osteophyte load correlated with cortical thickness for cases ($R^2=0.25$) but did not for controls ($R^2=0.04$). CTh in ROI=1.2–0.01*osteophyte load, $p<0.0001$, adj $R^2=0.25$

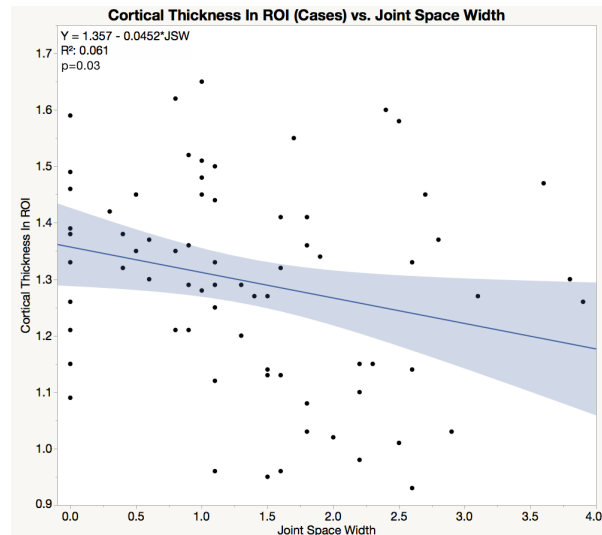


Figure 4.3: JSW correlated with cortical thickness for cases ($R^2=0.06$) but did not for controls ($R^2=0.01$). CTh in ROI=1.4–0.05*mJSW, $p=0.03$, adj $R^2=0.06$

Hip pain alone had a sensitivity for THR of 44.6% (33.8–55.9), specificity 89.7% (84.4–93.3), with the associated predictive values (PPV 63.5% (49.9–75.2), NPV 80.1% (74.1–85.0) PLR 4.3 (2.6–7.1) NLR 0.6 (0.5–0.76). All imaging investigations ranged in clinical utility index from good to excellent, see *Table 4.3*. I considered the utility of the RCS clinical pathway in 52 of these patients presenting with baseline hip pain to a clinician. By requesting imaging and receiving a grading report of “definite osteoarthritis” (2D radiographic K&L score of ≥ 2), the primary care physician would correctly identify 85% (28/33) who would go on to require THR for osteoarthritis within 3 years and reassure 95% (18/19) that THR would not be performed. In clinical practice, knowing that the patient K&L score is ≥ 2 is excellent for confirmative case finding, the patient may be destined for THR (positive clinical utility index 0.82 (0.70, 0.94)), and good for screening, ruling out a patient who is unlikely to require a THR (negative clinical utility index 0.74 (0.62, 0.87)).

Measure (+radiographic)	Sensitivity	Specificity	PPV	NPV	PLR	NLR
+ 3D CTh*	81.8% (65.6–91.4)	94.7% (75.4–99.1)	96.4% (82.3–99.4)	75.0% (55.1–88.8)	15.5 (2.3–105.5)	0.2 (0.1–0.4)
+ 2D mJSW**	75.8% (59.0–87.2)	89.5% (68.6–97.1)	92.6% (76.6–97.9)	68.0% (48.4–82.8)	7.2 (1.9–27.1)	0.27 (0.1–0.5)
+ 2D K&L***	84.8% (69.1–93.3)	94.7% (75.4–99.1)	96.6% (82.8–99.4)	78.3% (58.1–90.3)	16.1 (2.4–109.2)	0.2 (0.1–0.4)

PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CTh, cortical thickness; mJSW, minimum joint space width; K&L, Kellgren & Lawrence score; *for females by ≥ 1.2 mm and males ≥ 1.29 mm; **for females by ≤ 1.24 mm and males ≤ 1.73 mm; ***outcome by a K&L grade of ≥ 2

Table 4.3: Effects of imaging in the osteoarthritis clinical pathway; prediction of total hip replacement by different imaging modalities in 52 individuals presenting with hip pain

Even simple measures had clinical utility: a mJSW ≤ 1.24 mm for women and ≤ 1.73 mm for men would correctly identify 76% (25/33) and reassure 89% (17/19). In individuals with a CTh of ≥ 1.20 mm for women and ≥ 1.29 mm for men would correctly identify 82% (27/33) and reassure 95% (18/19).

Shape modes *Chapter 3 Section 3.1.7* did not predict THR (see *Appendix E*).

4.1.2 Results Predicting Hip Pain

Structural measures of osteoarthritis were all strongly associated with prevalent baseline hip pain, and these results are given irrespective of whether the study participant underwent a THR or not. Odds ratios of K&L grade for hip pain on the correct side increased with increasing radiographic severity, see *Figure 4.4* and *Table 4.4*. Moderate/Severe grading (50 hips) yielded an OR of 12.22 (6.00–25.46, $p < 0.0001$) for prevalent “correct side” hip pain. Minimum joint space width was associated with hip pain (Figure 3, OR 2.7 per SD narrowing 95%CI 1.6, 4.4). Similarly, CTh was associated with hip pain (OR 2.1 per SD thickening 95%CI 1.5, 3.1). Odds ratios of K&L grade for concurrent ipsilateral hip pain were appropriate to damage severity, see *Figure 4.4*. With reference to “no osteoarthritis” (K&L grade 0), the OR of concurrent hip pain, see *Table 4.4*. Similarly, CTh was associated with hip pain (OR 2.1 per SD thickening 95%CI 1.5, 3.1) and mJSW, in particular being strongly associated with hip pain (OR 2.7 per SD narrowing 95%CI 1.6, 4.4). In addition, multiple linear regression was calculated to predict mJSW based on age, sex and hip pain (replicating[327]). A significant regression equation was found ($F(3,454)=26.1$ $p < 0.0001$) with an R^2 of 0.15. Participants’ predicted mJSW was equal to $3.12\text{mm} - 0.35(\text{pain}) - 0.02(\text{age}) + 0.22(\text{sex})$ where pain was coded as 1=yes, 2=no, age was measured in years and sex was coded as 1=male, female=2. mJSW was 0.35mm thinner in those with hip pain, males had 0.22mm wider mJSW than females.

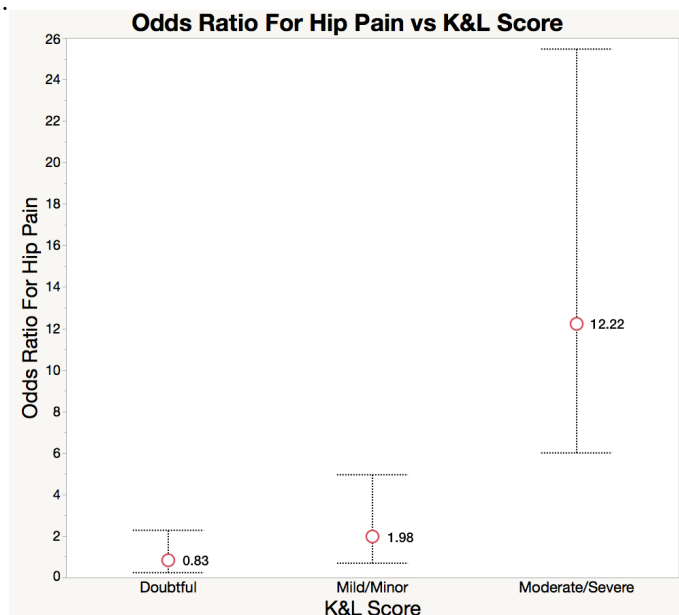


Figure 4.4: Odds ratio for hip pain vs K&L score in terms of radiographic classification, irrespective of whether the participant was destined for THR or not.

Doubtful (66 hips), Mild (45 hips), Moderate/Severe (50 hips)

K&L Classification	Number of Hips	K&L Grade	OR (95% CI)	P Value
Doubtful	66	1	0.83* (0.24–2.28)	0.7363
Mild	45	2	1.98* (0.69–4.95)	0.1914
Moderate/Severe	50	3+4	12.22* (6.00–25.46)	<0.0001
Moderate***	40	3	8.92 (4.10–19.42)	<0.0001
Severe***	10	4	50.78 (10.05–256.58)	<0.0001
mJSW	458	–	2.68** (1.64–4.36)	<0.0001
CTh	258	–	2.14** (1.46–3.12)	<0.0001

*versus none **per SD narrowing (mJSW) or thickening (CTh) ***individual K&L grades

Table 4.4: Hip Pain Odds Ratio Data

Histograms, as seen in *Figure 4.5*, show the association between narrowed JSW and hip pain (lower panel) irrespective of whether patients were destined for THR for osteoarthritis (hashed, within lower histogram). The upper panel shows the usual distribution of mJSW in patients without hip pain. Note the similar right skew distribution of mJSW in those who had not yet developed hip pain at baseline but were destined for THR (hashed, upper).

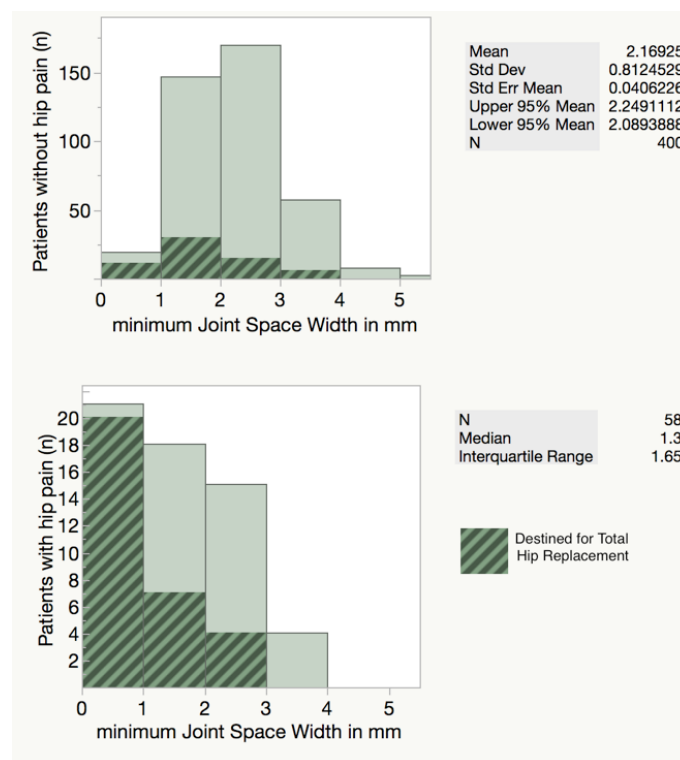


Figure 4.5: JSW And Hip Pain Association Histograms

4.2 Results Of The 3D Printing Study

Hypothesis 3: The 3D printed model of the SPM osteoarthritis ROI result will help with the understanding of osteoarthritis disease features.

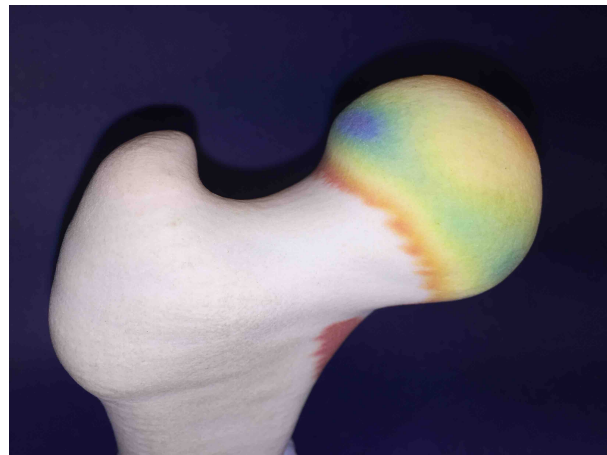
A 3D printed model allowed us to visualise how cortical thickening in osteoarthritis (observed in the AGES study) related to functional anatomy. I was able to attach the 3D printed femur model to an anatomical hip joint model with integrated labrum and prosthetic ligaments to observe and study where the areas of cortical thickening may have occurred. This enabled us to visualise complex geometries of hip joint anatomy to better understand the ROI of cortical bone thickening. Valdecasas et al. concluded that physical models provide an optimal tool for the understanding of anatomy.[328] I decided to combine the 3D printed SPM ROI model with a multi-component acetabular/pelvic model to be used as an analogous visual aid.

4.2.1 3D Printed Femur

After the 3D printing process, see *Chapter 3 Section 3.2*, was completed, the printed model, see *Figure 4.6*, was the result. A 3D hip joint model complete with ligaments was obtained, see *Figure 4.7*.



(a) *View From Above*



(b) *Side View*

Figure 4.6: 3D Printed Femur

4.2.2 3D Hip Joint Model

The anatomical model was the 66fit Anatomical Life Size Human Hip Joint with flexible artificial ligaments, see *Figure 4.7*. Because I did not need to connect the ligaments to the femur of the 3D printed model (with the statistically significant OA ROI coloured surface printed on), it was decided that they were to be removed in order to not obstruct the view of the socket of the acetabulum. The plastic femur was removed to make way for the 3D printed femur and the entire pelvis was attached to an existing skeleton model that was present in the lab, the final arrangement of the model can be seen in *Figure 4.8*.



Figure 4.7: Anatomical Hip Joint Model With Attached Labrum And Ligaments

Images taken from <http://www.66fit.co.uk/66fit-human-hip-joint-anatomical-model.html>



Figure 4.8: Adapted Arrangement Of Pelvic Hip Joint Model

4.2.3 Combining The 3D Printed Model With Hip Joint Model

Looking at the two models together and manipulating the printed femur at various angles allowed me to visualise how cortical thickening in osteoarthritis related to functional anatomy (*Figure 4.9*). As can be clearly seen, the blue areas of maximal (approx. 70%) thickening correspond almost exactly with the superior contact surface of the acetabular/labral margin.



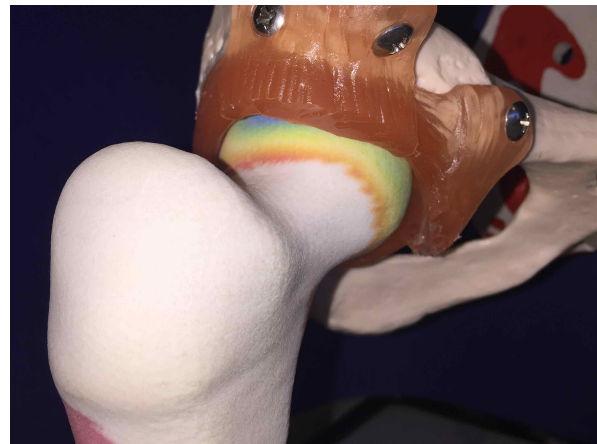
(a) Hip Joint Model



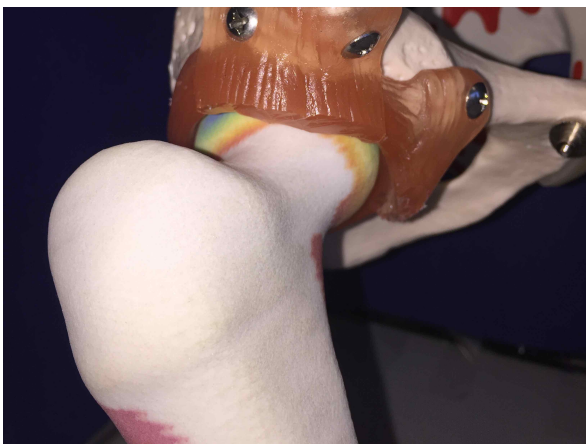
(b) 3D Printed Femur Introduced



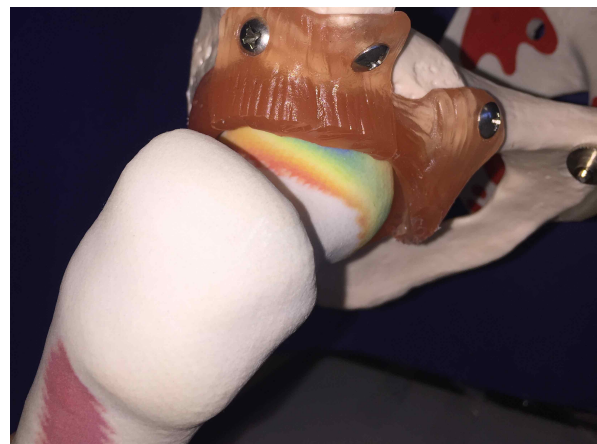
(c) 3D Printed Femur Inserted Into Hip Socket



(d) Leg Parallel To Body



(e) Leg In Front Of Body



(f) Leg Behind Body

Figure 4.9: Various Angles And Views Of The 3D Printed Femur And Hip Model

4.3 Results Of The Mindways Ageing Study

Hypothesis 4: The distribution of cortical bone in the femoral head will become “osteoarthritic” with ageing which will manifest as regional “thickening”.

I wanted to investigate if cortical bone thickening is an inevitable consequence of ageing or only in select osteoarthritis prone individuals. By using the *JMP* statistical software package and implementing the statistical techniques, mentioned in *Section 3.3.5*, I was able to produce the following results, see *Figure 4.10*.

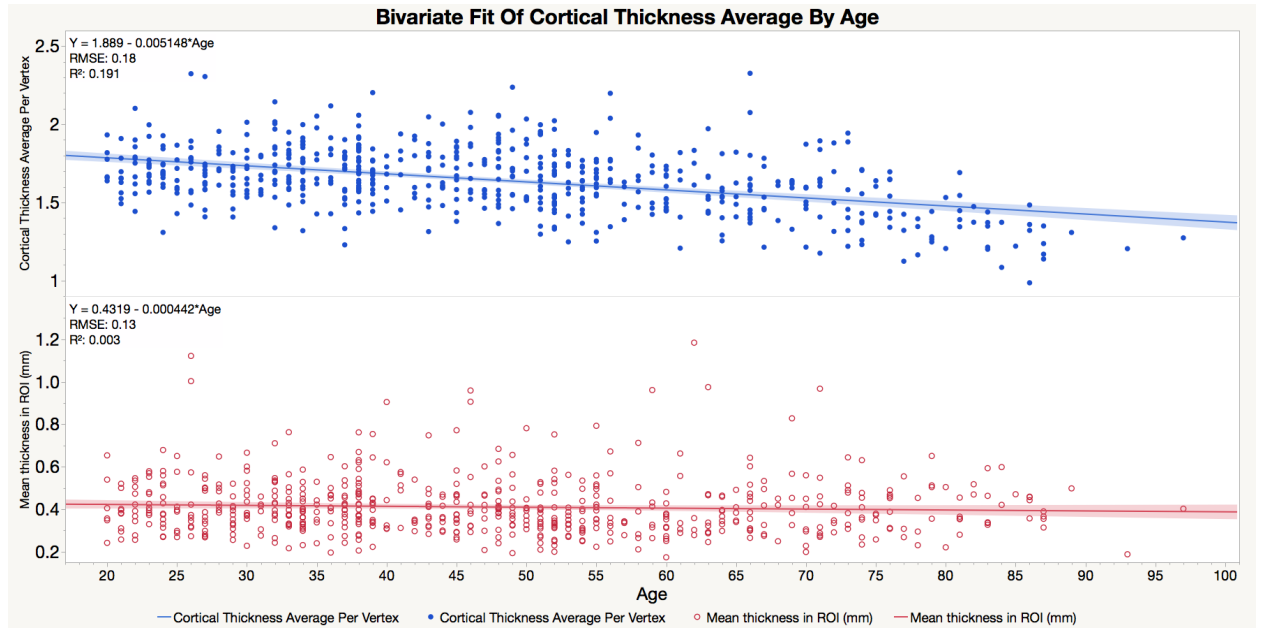


Figure 4.10: Standard Linear Model Of Cortical Thickness Average By Age

Upper panel (blue) is average across whole femur and lower panel (red) is the change in the osteoarthritic-specific ROI.

From this initial observation I found that the overall femoral CTh (average per vertex) generally decreases as age increases, with a linear function of $y = 1.89 - 0.0051 \times \text{Age}$, an R^2 value of 0.19 and a root mean square error (RMSE) value of 0.18. When comparing this to the results of the mean thickness in ROI, I found that there was no significant change with increasing age and a linear function of $y = 0.43 - 0.0004 \times \text{Age}$, an R^2 value of 0.003 and a RMSE value of 0.13.

However, as previously explained, my data is non-linear so quadratic modelling (quadratic regression) would allow for a more accurate interpretation to see how different CTh measurements change depending on different ages, which is exactly what I implemented next, see *Figure 4.11*.

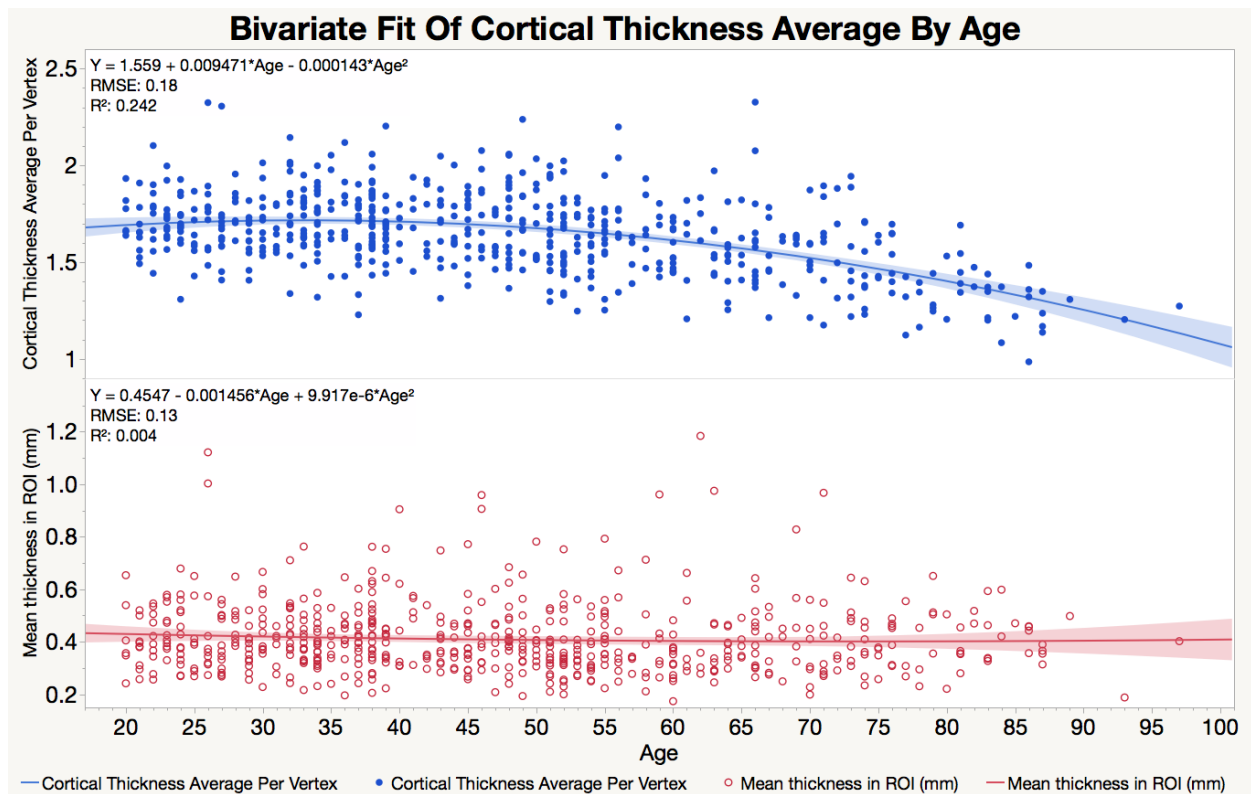


Figure 4.11: Quadratic Model Of Cortical Thickness Average By Age

From the quadratic modelling I confirmed (as with standard linear modelling) that the CTh average per vertex generally decreases as age increases, but there is a sharper decrease after the age of 50 as expected (in-part due to menopause), see *Section 1.6.3*. I found a quadratic function of $y = 1.56 + 0.009 \times \text{Age} - 0.0001 \times \text{Age}^2$, an R^2 value of 0.242 and a RMSE value of 0.18. When comparing this to the results of the mean thickness in ROI, I found that there was generally no significant change with increasing age but a wider range of mean thickness in ROI at 80+ years. It also had a quadratic function of $y = 0.45 - 0.001 \times \text{Age} + 0.000001 \times \text{Age}^2$, an R^2 value of 0.004 and a RMSE value of 0.13.

Using the *JMP* software package, I was able to select a specific subject and understand what CTh average per vertex value and mean thickness in ROI value they had and visually highlight it on the quadratic graph.

As an example, I chose to investigate 3 subjects from a variety of areas around the graph:

The first subject was a 62 year old with remarkably average (1.61mm) femoral head CTh vs age, yet had the highest (1.18mm) mean thickness in the OA-ROI vs age (*Figure 4.12*).

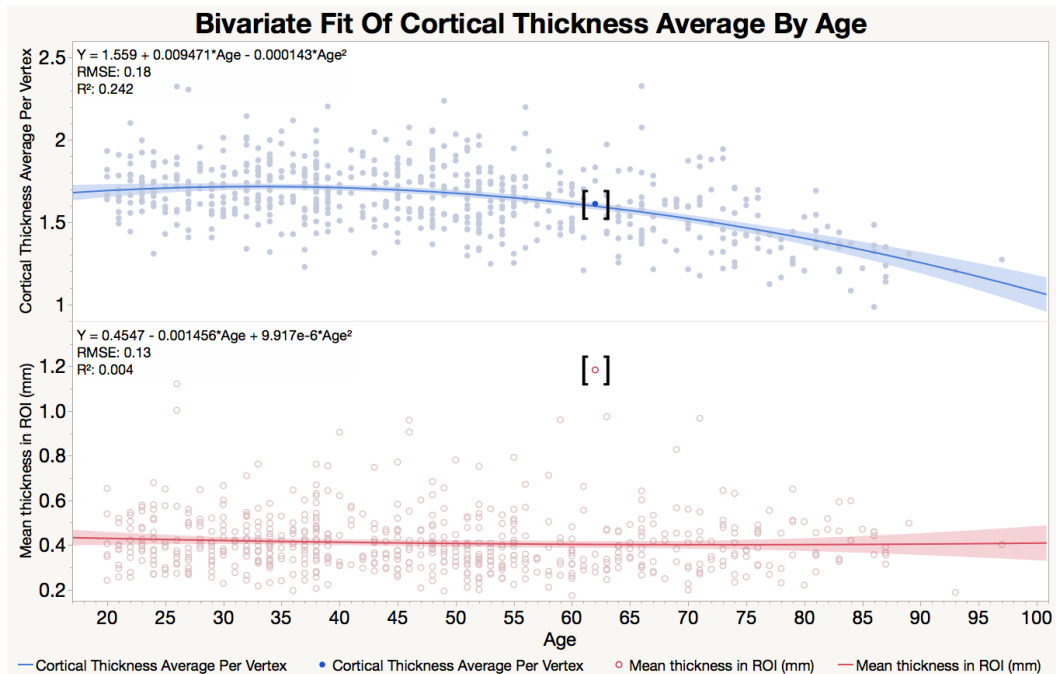


Figure 4.12: 62 Year Old Subject; CTh Average Per Vertex=1.61 And Mean ROI=1.18

CT data of this individual illustrates the focal thickening of the femoral head. So I would classify this subject as one who is likely to develop clinical osteoarthritis in the future (*Figure 4.13*) with possible likelihood of requiring THR.

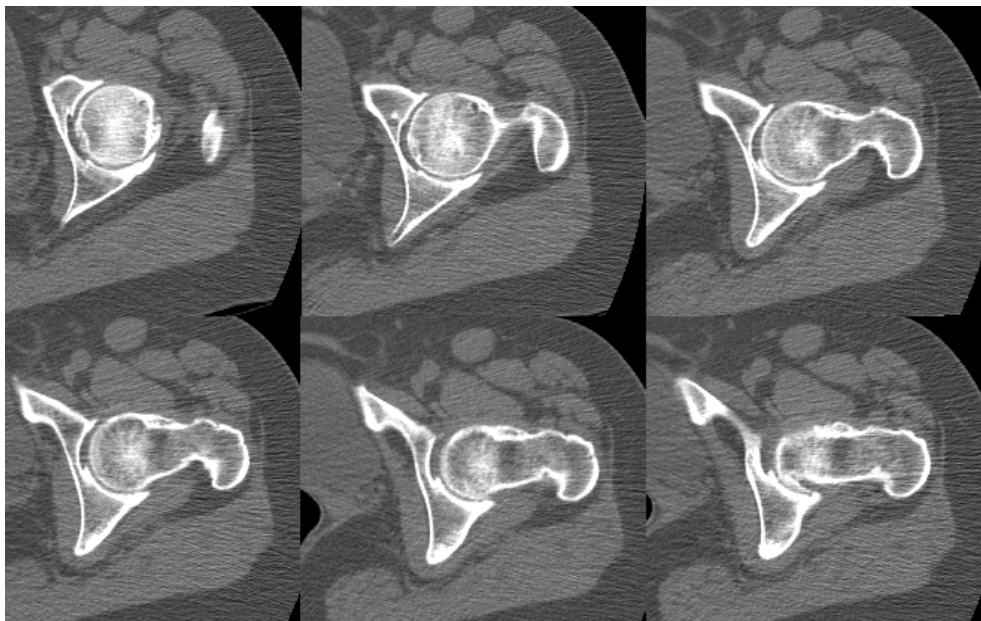


Figure 4.13: CT Data Of 62 Year Old Subject

The second subject was a 66 year old who had the highest average (2.32mm) femoral head CTh, yet had only slightly above average (0.60mm) mean thickness in ROI vs age (*Figure 4.14*). Therefore I consider that generalised cortical thickening is not invariably associated with thickening in the OA-ROI.

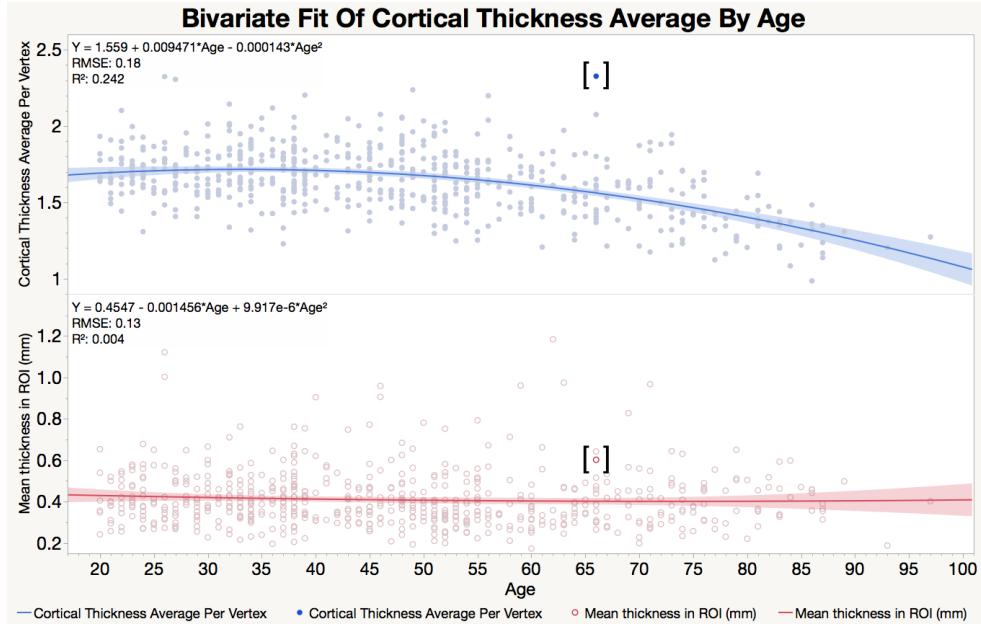


Figure 4.14: 66 Year Old Subject; CTh Average Per Vertex=2.32 And Mean ROI=0.60

The third subject was a 26 year old with modestly elevated (1.89mm) femoral head CTh but with very thickened (1.12mm) osteoarthritis ROI despite her young age (*Figure 4.15*). I consider that the discovery of such focal thickening in the OA-prone regions, despite modest overall cortical thickness could indicate a potential novel biomarker for very early OA.

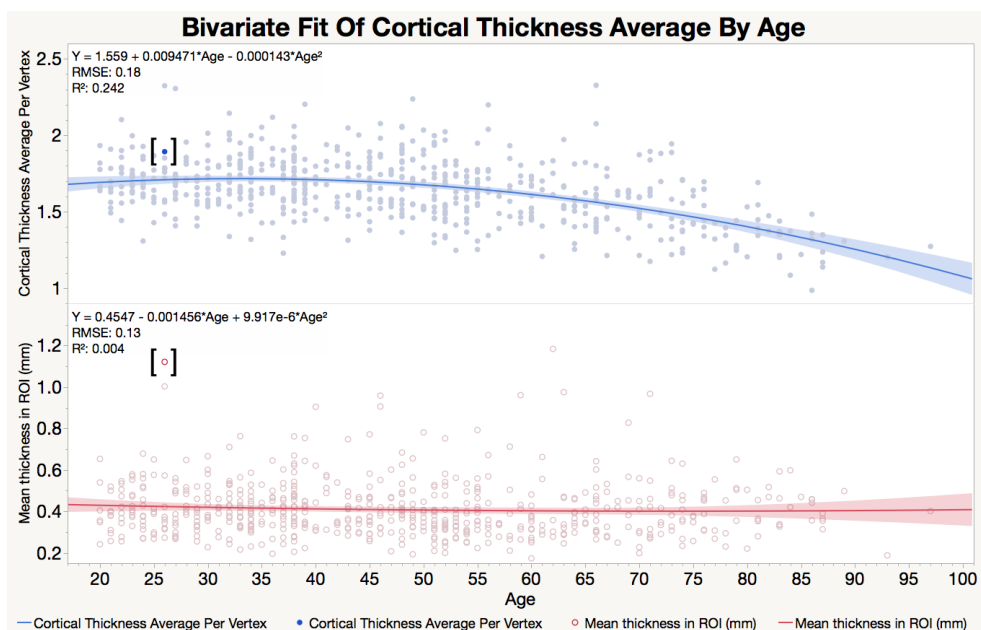


Figure 4.15: 26 Year Old Subject; CTh Average Per Vertex=1.89 And Mean ROI=1.12

Chapter 5

Discussion

If findings from this large population-based Icelandic prospective study are generalisable, then imaging seems to be a vital part of the effective management of patients presenting with hip pain. Unlike reliance on patient symptoms alone, all imaging measures tested unequivocally predicted THR within 3 years for symptomatic osteoarthritis, irrespective of the presence of baseline hip pain. By focusing on the poor correlation between imaging findings and pain, guideline writers may have missed where the true utility of imaging in osteoarthritis resides. I suggest that clinicians should adhere to the 2017 RCS recommendations which allow judicious use of AP radiographs in adults with hip pain. Any disutility of imaging findings among some individuals with structurally damaged joints who exhibit little pain or can tolerate pain, or those other individuals with hip pain who have little radiographic hip osteoarthritis (perhaps, because they have another reason for hip pain), can be borne in mind by the referrer in receipt of the radiology report but are not a valid reason to alter this recommendation.[201] AP radiographs are an effective diagnostic tool and permit the timely identification of those patients with symptoms who would benefit from surgical referral. My findings support the use of diagnostic imaging in the clinical pathway for adults presenting with symptoms of hip osteoarthritis, in keeping with the 2017 ‘Pain arising from the hip’ guidelines of the Royal College of Surgeons. My results do not support guidelines which deter clinicians from requesting all forms of imaging in people with hip pain (such as the NICE osteoarthritis guidelines, new EULAR imaging in osteoarthritis guideline and Osteoarthritis Patient Management tool of the Arthritis Alliance of Canada). In my study, any radiographic indicator of osteoarthritis accurately discriminated patients destined for THR.

Why has downplaying the predictive value of radiological osteoarthritis hip features become widespread?[109] It seems clear that older patients will have hip pain for many reasons (e.g. trochanteric bursitis, soft tissue or referred pain) unrelated to radiographic appearances, and equally clear that some patients will tolerate osteoarthritis changes in the hips without needing surgery, due to differing pain perception or patient/surgeon inclination.

We found that 2D hip radiographs were diagnostically useful, and would appear to fulfil the validity questions for a diagnostic test and Quantitative Imaging Biomarkers Alliance (QIBA) criteria of an imaging biomarker for disease (evidence-based medicine toolbox,[329] QIBA <https://www.rsna.org/QIBA/>). I found that 2D radiograph grade performed very well in predicting the need for a surgical solution to hip pain (cross-validated AUC 0.88). Hip pain alone was less predictive (AUC 0.63). Optimum performance came from a model containing pain, 2D grading of osteoarthritis and 3D cortical thickness (AUC of 0.90). Many factors determine the decision to refer to surgeons or to offer THR, but simple imaging findings are a key component of the patient pathway. For patients presenting with hip pain by WOMAC questioning in my study, a finding of definite radiological osteoarthritis would allow their clinician to correctly predict 85% that were likely to undergo THR within an average of 3 years. Conversely, only 15% of patients had THR without baseline radiological osteoarthritis. I have no follow-up imaging to know the rapidity of structural changes in those individuals, but I speculate that they also would have developed radiographic osteoarthritis. Since THR is not performed in asymptomatic individuals, it is noteworthy that more than half (41/74) of those who would undergo THR had no hip pain at baseline suggesting relatively rapid development of symptoms from joints that already bear structural hallmarks of significant osteoarthritic disease. A phenotype of hip osteoarthritis, before end-stage joint failure and hip pain might exist, amenable to emerging therapies. In this respect, my work adds further useful data; concerning the 3D features that typify painful and surgically-destined osteoarthritis.

Irrespective of the underlying cause of osteoarthritis, the uniform and characteristic phenotype of femoral cortical thickening shown here was useful for predicting THR. Arbitrarily splitting the imaging findings into “atrophic” (with no osteophytes) and “hypertrophic” (with osteophytes), based on 3D osteophyte load,[2] made no difference to the discriminatory ability of cortical thickness for THR, indicating a unified “end-stage” phenotype of osteoarthritis destined for surgery, and one that is clearly associated with pain in that hip. In

osteoarthritis, cartilage is lost, osteophytes begin to form at the edge of the articular cartilage and the subchondral bone plate underneath is thickened.[330] Coronal plane radiographs of osteoarthritic individuals are characterised by narrowing of the hip joint space, osteophytes and femoral head bone thickening (subchondral sclerosis). These classic disease features are strong predictors of osteoarthritis progression and THR but require careful assessment and formal reporting of plain radiographs of the hips, something that I have found is not always done. Irrespective of whether the hips had become painful, 3D focal bone thickening was a strong predictor of eventual THR (OR 5 for each SD thicker). The location of the characteristic bone thickening, see *Figure 3.7*, strongly supports the “wear and repair” concept of hip osteoarthritis, being prominent at the femoral contact area with the acetabular labrum, a site of high contact pressure at the articular margin where osteophytes form. A crescent of thickening occurred in areas normally loaded during sitting, standing and walking. JSN explained only 5% of the variance in cortical thickness, and then only in patients destined for THR. This suggests that mechanisms other than cartilage loss are at play in determining the thickening observed. This adds to a growing literature highlighting the importance of bone in osteoarthritis pathogenesis. Osteophytes only accounted for part of the relationship between increasing CTh and worsening osteoarthritis grade $R^2=0.25$. [293] Bone structure itself has become increasingly appreciated as integral to osteoarthritis pathogenesis,[331] with biomarker analyses indicating a link between subchondral bone characteristics (known to be thickened in osteoarthritis[330]) and overlying cartilage loss.[332] Bone changes are not only seen at the final stage of the disease, but at the onset.[333] leading some to suggest that cartilage damage could be initiated by abnormal subchondral bone.[334, 335] Marginal thickening of subchondral bone is presumably multifactorial: possibly from nascent osteophytes, excess loading on the joint itself due to the subject’s joint shape or a previous trauma. Studies are now warranted that look at whether such features are present in people many years prior to developing clinical osteoarthritis; key questions are whether they potentially predict osteoarthritis onset, track joint degradation or can be used to evaluate the effectiveness of therapy.[336]

A formally graded 2D image (K&L method) in place of my advanced 3D CT bone thickness measure gave equivalent performance (AUC 0.85 vs AUC 0.87 $p=0.49$) for less radiation. While I used digital radiographs from CT, plain AP radiographs (referred to in the NICE 2017 Hip Pain pathway) are nearly equivalent in routine clinical practice. Formal grad-

ing of hip radiographs in clinical practice is essential to achieve this level of accuracy, but such assessments are rarely done despite long-established validity, and I do question that part of the RCS 2017 pathway which states that, “referral should be independent of the radiographic grade of arthritis”. TDT audited radiology reports and found only 53% reliability from non-graded reports in allowing primary care doctors to determine which patients should be referred for orthopaedic surgery assessment, 4% with no comment at all, 10% of reports that could have led to missed referral and 33% of reports that could have led to inappropriate referral.[292] Since formal K&L grading can be time consuming,[337] I tested a simple narrowest superior joint space width (mJSW) measure which takes moments using any modern PACS reporting station. Indeed, change in mJSW is the FDA-approved, validated method for assessing disease progression;[338] I found mJSW highly predictive of THR in symptomatic individuals (AUC 0.80 vs AUC 0.87 of formal K&L grading, $p=0.002$); I propose that this measure could be used in clinical practice easily.[291] Unlike Dougados et. al, whose patients were selected for a therapeutic trial, I found a robust association between pain and mJSW,[327] although obviously there are many unmeasured reasons for JSW to differ widely between individuals.[337] While semi-automated 3D bone mapping from CT has no prerequisite for radiological expertise, nor for subjective assessment of CT images (important due to high K&L intra and inter-observer variability[339, 340]). Radiation dose, availability, processing steps and cost of CT will clearly favour 2D radiographs.

A full cross-sectional cohort study design for diagnostic accuracy (imaging predicting surgery) was not feasible, which is a limitation.[341] ROC analysis in matched case-control studies may necessitate adjustment for potentially confounding covariates,[342] but I used standard unadjusted research methods. Given the fairly low absolute THR rate in the whole cohort, from which my nested case-control study was derived, it is a future priority (when sufficient time has elapsed from recruitment) to select a further nested sample of all patients presenting with baseline hip pain from which to gather imaging diagnostic accuracy data.[341] I lack information from clinical examination of the hip in the participants and a lack of data on patient surgical/conservative treatment preference. I used supine CT images to create digital radiographs which are subtly different from the standing 2-view plain radiographs used in routine clinical practice; hence, the cut-off values of mJSW cannot be applied to ordinary radiographs. Iceland has a very high prevalence (five-fold higher than in southern Scandinavia) of radiological primary hip osteoarthritis, particularly noticeable

for individuals younger than 70 years.[62] Hence, generalisability beyond Icelandic population is unknown. However, this study was the validation of an original discovery made in a UK cohort[29] so it is likely that the findings are robust at least to the UK and Iceland.

The research findings explain why simple planar radiological features of hip osteoarthritis are important; they usefully reflect the underlying 3D mechanics of joint failure that I have quantified using more complex CT methodology. In light of the findings and in agreement with Royal College of Surgeon Hip pain management guidelines, I suggest that simple planar imaging assessment for structural features of osteoarthritis in individuals with hip pain is useful to confirm the diagnosis and determine suitability for onwards referral to secondary care.

5.1 Conclusions Of The AGES Study

If findings from this large population-based Icelandic prospective study are generalisable, then imaging is a vital component for patient stratification. Unlike reliance on patient symptoms alone, all imaging measures tested unequivocally predicted THR within 3 years for symptomatic osteoarthritis, irrespective of the presence of baseline hip pain. By focusing on the poor correlation between imaging findings and pain, guideline writers have missed where the true utility of imaging in osteoarthritis resides. I suggest that clinicians should adhere to the 2017 RCS recommendations which allow judicious use of AP radiographs in adults with hip pain. Any disutility of imaging findings among some individuals with structurally damaged joints who exhibit little pain or can tolerate pain, or those other individuals with hip pain who have little radiographic hip osteoarthritis (usually because they have another reason for hip pain) can be borne in mind by the referrer in receipt of the radiology report but are not a valid reason to alter this recommendation. AP radiographs are an effective diagnostic tool and permit the timely identification of those patients with symptoms who would benefit from surgical referral.

Signs of osteoarthritis from an AP radiograph unequivocally predicted THR for osteoarthritis, whether or not pain had become apparent, whereas hip pain alone was a poor to marginal predictor (AUC 0.70). Using all available imaging parameters in patients with hip pain gave excellent prediction (AUC 0.90). In a typical clinical pathway, knowing that the patient had radiographic osteoarthritis was “excellent” for confirmatory case finding; i.e. the pa-

tient may be destined for THR (positive clinical utility index 0.82 95%CI; 0.70, 0.94), and “good” for screening; i.e. reassuring that the patient was unlikely to require a THR within the coming years (negative clinical utility index 0.74; 0.62, 0.87). In agreement with RCS guidance, the results of an AP radiograph in patients with hip pain would have permitted accurate stratification of the need for referral for surgery from primary care. Formal grading of simple AP radiographs by a radiologist was as effective as novel 3D CT methods in disease prediction.

5.2 Conclusions Of The 3D Printing Study

The 3D printed model of the SPM osteoarthritis ROI result from the AGES study helped with the understanding of osteoarthritis disease features and allowed me to visualise how cortical thickening in osteoarthritis related to functional anatomy. By attaching the 3D printed femur model to an anatomical hip joint model I was able to observe and study where and why the areas of cortical thickening may have occurred. Individual patient specific femur models mapping in colour the area of the joint that varies (either in thickness or joint space narrowing) compared to an average population could potentially be used as a visual aid to plan the patients personalised osteoarthritis therapy (weight loss, exercise, pharmaceutical intervention etc). Patients appreciate visualising what is happening in their joints and, these 3D models may provide patients with an accessible and easy to understand view of their anatomy and diagnosis.

5.3 Conclusions Of The Mindways Ageing Study

With the Mindways ageing study I was able to use the CBM technique to show generalised cortical thinning with ageing, but complete preservation of the OA-specific ROI throughout life. Some subjects had markedly elevated cortical thickness in the hip-OA specific 3D mapped region, and I postulate that they are individuals who are likely to develop clinically or even surgically relevant osteoarthritis.

At the start of this work, I aimed to establish phenotypes of hip structure that are predictive of clinical and surgically-destined osteoarthritis as potential novel biomarkers.

My studies have confirmed, unequivocally that 2D imaging has clinical utility in predicting

total hip replacement in those with hip pain. Future work in this field will be to sample all patients with baseline WOMAC hip pain in the AGES cohort and follow them up, since at present I only selected those destined for THR (see page 99 and [341]). The work also re-established the strong relationship between OA imaging findings and prevalent hip pain.

I established that the cortical bone thickening osteoarthritic phenotype (first identified in a UK cohort[29]), is very strongly predictive of incident THR in those with hip pain, and much more predictive than relying on symptoms alone. Further work will need to identify whether this holds true for younger populations, meaning that a long-term prospective study is needed using CT, potentially recontacting the Mindways cohort patients as they age. Further work will also need to use finite element modelling and other biomechanical approaches to confirm my assertion that the thickening is the result of focal wear and repair mechanisms. Finally, I provide strong evidence for the central role of subchondral thickening of the femoral head in osteoarthritis evaluation and pathogenesis.

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Appendix A

Summary Of Osteoarthritis Treatment Strategies

	Outcome	Comments
Lifestyle modification		
Weight loss, ⁹⁵⁻⁹⁸ exercise ⁹⁹ (strength and aerobic capacity)	Symptom improvement and reduced risk of symptomatic osteoarthritis MRI and biochemical marker evidence of structural modification	Potential role as primary prevention strategy
Surgical modification of joint biomechanics		
Periarticular osteotomy ^{100,101} (to correct mechanical axis of knee or orientation of acetabulum)	Established technique for improvement of symptoms and probably joint survival	Suggested potential for cartilage regeneration after these procedures
Debridement of FAI lesions ¹⁰²	Symptom improvement sustained beyond 5 years	Small cohort studies only; structural modification not yet shown; RCTs underway
Joint distraction ¹⁰³ (6–12 weeks)	Sustained symptomatic improvement with evidence of cartilage regeneration	Best evidence so far that cartilage can regenerate in an osteoarthritic joint
Regenerative surgical techniques		
Microfracture of subchondral bone ¹⁰⁴	Slight improvement in pain and defect filling	Produces mechanically inferior fibrocartilage rather than hyaline cartilage
Cell-based therapies ^{104,105} (autologous chondrocyte implantation)	Slight improvement in pain and defect filling	Might provide more durable repair tissue than microfracture but further studies are needed; technique is expensive
Pharmaceutical: targeting cartilage degradation		
Glucosamine and chondroitin, ¹⁰⁶ hyaluronic acid ¹⁰⁷	Meta-analyses do not show improvement in symptoms or structure over placebo	Conflicting results from different studies
Doxycycline ¹⁰⁸	Structural modification but no symptomatic benefit	Limited by side-effects
FGF-18 (intra-articular) ¹⁰⁹	Structural modification but no symptomatic benefit	Primary outcome measure of structural change in medial compartment not shown
Pharmaceutical: targeting bone remodelling		
Strontium ranelate ¹¹⁰	Improvement in symptoms and structure	Limited by side-effects
FAI=femoroacetabular impingement. RCT=randomised controlled trial. FGF=fibroblast growth factor.		
Table : Summary of treatment strategies that have shown potential disease-modifying properties		

Appendix B

AGES Statistical Parametric Analysis Matlab Script

This Matlab script was written by Graham M Treece, adapted and commented by me for the AGES dataset.

```
1 %% variables which control overall behaviour
2 pthresh = 0.05; % statistical threshold
3 blank_nonsig = true; % grey or washed out colours
4 compact = 6;
5 absolute = false; % false = percent changes & true =
6 % absolute changes
7 cmap = 4;
8 do_cbm = [1:4]; % thickness, mass, density,
9 % trabecular density (all)
10 %do_cbm = [1]; % only thickness
11 %do_cbm = [2]; % only mass
12 %do_cbm = [3]; % only density
13 %do_cbm = [4]; % only trabecular density
14
15 %% set up some limits for the colourbars in the plots for HIP PAIN
16 % if (absolute)
17 % thick_clim1 = [-0.3 0.1]; % cTh
18 % mass_clim1 = [-25 0]; % CMSD
19 % density_clim1 = [-40 0]; % CBMD
20 % trab_clim1 = [-60 25]; % ECTD
21 % else
22 % thick_clim1 = [-40 4]; % cTh
23 % mass_clim1 = [-40 4]; % CMSD
24 % density_clim1 = [-40 4]; % CBMD
25 % trab_clim1 = [-2454.9 2411.7]; % ECTD
26 % end
27
28 %% set up some limits for the colourbars in the plots
29 % if (absolute)
30 % thick_clim1 = [0 0.45]; % cTh [0 0.45];
31 % mass_clim1 = [-20 60]; % CMSD [-20 60];
32 % density_clim1 = [-40 110]; % CBMD [-40 110];
33 % trab_clim1 = [-60 80]; % ECTD [-60 80];
34 % else
35 % thick_clim1 = [0 70]; % cTh [0 70];
36 % mass_clim1 = [-10 70]; % CMSD [-10 70];
37 % density_clim1 = [-5 20]; % CBMD [-5 20];
38 % trab_clim1 = [-40 80]; % ECTD [-40 80];
39 % end
40
41 %% set up mean value colorbar limits and some unit variables
42 thick_clim2 = [0 5];
43 mass_clim2 = [0 600];
44 density_clim2 = [0 1200];
45 trab_clim2 = [0 350];
46 thick_units = {'(mm)'};
47 mass_units = {'(mg/cm^2)'};
48 density_units = {'(mg/cm^3)'};
49 trab_units = {'(mg/cm^3)'};
50 percent_units = {'(%)'};
```

```

51
52 %% load canonical
53 if ~exist('avsurf')
54     avsurf = SurfStatReadSurf( 'canonical.femur.5580.wrl' );
55 end
56
57 [file, id, ok, side, bmd_a, bmd_b, hu, inblur, outblur, bmd, replace, ...
    age, replace_age, sex, height, weight, hp, replace_side, KL, JSW, ...
    OP, m{1}, m{2}, m{3}, m{4}, m{5}, m{6}] = textread( 'details.txt', ...
    ['%s %f %f %s %f %f %f %f %f %f %s %f %f %s %f %f %f %s %f %f %f %f ...
    %f %f %f %f %f'] );
58
59 %% remove any redundant values
60 ok = ok & (age~-1);
61 file = file(ok);
62 id = id(ok);
63 side = side(ok);
64 bmd_a = bmd_a(ok);
65 bmd_b = bmd_b(ok);
66 hu = hu(ok);
67 inblur = inblur(ok);
68 outblur = outblur(ok);
69 bmd = bmd(ok);
70 replace = replace(ok);
71 age = age(ok);
72 replace_age = replace_age(ok);
73 sex = sex(ok);
74 height = height(ok);
75 weight = weight(ok);
76 hp = hp(ok);
77 replace_side = replace_side(ok);
78 KL = KL(ok);
79 JSW = JSW(ok);
80 OP = OP(ok);
81 shape_modes = 6;
82
83 for sm=1:shape_modes
84     m{sm} = m{sm}(ok);
85 end
86
87 %% load CBM data
88 Y_thickness = SurfStatReadData( strcat(file,'thickness.bin') );
89 Y_trab = SurfStatReadData( strcat(file,'trab.density.bin') );
90 Y_density = SurfStatReadData( strcat(file,'density.bin') );
91
92 %% average over left and right if both exist
93 s=sort(unique(id));
94 subjects = max(size(s));
95 pairs=0;
96
97 for i=1:subjects
98     n = find(id==s(i));
99     if (max(size(n))>1) pairs = pairs+1; end;
100
101     mY_thickness(i,:) = mean(Y_thickness(n,:),1);
102     mY_trab(i,:) = mean(Y_trab(n,:),1);
103     mY_density(i,:) = mean(Y_density(n,:),1);
104     mid(i) = id(n(1));

```

```

105     mbmd_a(i) = bmd_a(n(1));
106     mbmd_b(i) = bmd_b(n(1));
107     mhu(i) = mean(hu(n));
108     minb(i) = mean(inblur(n));
109     moutb(i) = mean(outblur(n));
110     mbmd(i) = mean(bmd(n));
111     mreplace(i) = replace(n(1));
112     mage(i) = age(n(1));
113     mrage(i) = replace_age(n(1));
114     msex(i) = sex(n(1));
115     mheight(i) = height(n(1));
116     mweight(i) = weight(n(1));
117     mhp(i) = hp(n(1));
118     mKL(i) = mean(KL(n));
119     mJSW(i) = mean(JSW(n));
120     mOP(i) = mean(OP(n));
121
122     for j=1:shape_modes
123         msm{j}(i) = mean(m{j}(n));
124     end
125 end
126
127 Y_thickness = mY_thickness;
128 Y_trab = mY_trab;
129 Y_density = mY_density;
130 id = mid';
131 bmd_a = mbmd_a';
132 bmd_b = mbmd_b';
133 hu = mhu';
134 inblur = minb';
135 outblur = moutb';
136 bmd = mbmd';
137 replace = mreplace';
138 age = mage';
139 replace_age = mrage';
140 sex = msex';
141 height = mheight';
142 weight = mweight';
143 hp = mhp';
144 KL = mKL';
145 OP = mOP';
146 JSW = mJSW';
147
148 for s=1:shape_modes
149     m{s} = msm{s}';
150 end
151
152 clear mY_thickness mY_trab mY_density mid mbmd_a mbmd_b mhu minb moutb ...
    mbmd mreplace mage mrage msex mheight mweight mhp mKL mOP mJSW msm;
153
154 % densities are mg/cm^3, mass in mg/cm^2
155 for i=1:size(Y_density, 1)
156     Y_density(i,:) = (Y_density(i,:)-bmd_b(i))./bmd_a(i);
157     Y_trab(i,:) = (Y_trab(i,:)-bmd_b(i))./bmd_a(i);
158     Y_mass(i,:) = 0.1*Y_thickness(i,:).*Y_density(i,:);
159 end
160
161 % get mean values across all subjects

```

```

162 meanthick = mean(Y.thickness);
163 meandensity = mean(Y.density);
164 meanmass = mean(Y.mass);
165 meantrab = mean(Y.trab);
166
167 % set up figure defaults
168 set(0,'DefaultFontSize',14);
169 set(0,'DefaultAxesFontSize',14);
170
171 % do statistics
172 Replace = term(replace);
173 Age = term(age);
174 Sex = term(sex);
175 Height = term(height);
176 Weight = term(weight);
177
178 % added for hip pain SPM
179 HP = term(hp);
180
181 for sm=1:shape_modes
182     Mode{sm} = term(m{sm});
183 end
184
185 fig_num=1;
186
187 for i=do_cbm
188     if (i==1)
189         Y = Y.thickness;
190         figtext = {'CTh'};
191         if (absolute)
192             mY = 100*ones(size(meantrab));
193             units1 = thick_units;
194         else
195             mY = meanthick;
196             units1 = percent_units;
197         end
198         clim1 = thick_clim1;
199         clim2 = thick_clim2;
200         units2 = thick_units;
201         meanY = meanthick;
202     elseif (i==2)
203         Y = Y.mass;
204         figtext = {'CMSD'};
205         if (absolute)
206             mY = 100*ones(size(meantrab));
207             units1 = mass_units;
208         else
209             mY = meanmass;
210             units1 = percent_units;
211         end
212         clim1 = mass_clim1;
213         clim2 = mass_clim2;
214         units2 = mass_units;
215         meanY = meanmass;
216     elseif (i==3)
217         Y = Y.density;
218         figtext = {'CBMD'};
219         if (absolute)

```



```

220     mY = 100*ones(size(meantrab));
221     units1 = density_units
222 else
223     mY = meandensity;
224     units1 = percent_units;
225 end
226 clim1 = density_clim1;
227 clim2 = density_clim2;
228 units2 = density_units;
229 meanY = meandensity;
230 else
231     Y = Y_trab;
232     figtext = {'ECTD'};
233     if (absolute)
234         mY = 100*ones(size(meantrab));
235         units1 = trab_units;
236     else
237         mY = meantrab;
238         units1 = percent_units;
239     end
240     clim1 = trab_clim1;
241     clim2 = trab_clim2;
242     units2 = trab_units;
243     meanY = meantrab;
244 end
245 end
246 %%
247 % Calculate the actual statistics
248 M0 = 1 + Age + Sex + Weight + Height + Mode{1} + Mode{2} + Mode{3} + ...
      Mode{4} + Mode{5} + Mode{6};
249 slm0 = SurfStatLinMod(Y, M0, avsurf);
250 M = 1 + Replace + Age + Sex + Weight + Height + Mode{1} + Mode{2} + ...
      Mode{3} + Mode{4} + Mode{5} + Mode{6};
251 slm = SurfStatLinMod(Y, M, avsurf);
252 slm = SurfStatF( slm, slm0 );
253 [ pval, peak, clus, clusid ] = SurfStatP( slm );
254 cluster(i,:) = clusid>0;
255 mean.thickness(:,1) = mean(Y(:,cluster(i,:)),2);
256 pval.thresh = pthresh;
257
258
259 %% Tom Turmezei code snippet for ROI
260 %deliver a mask ROI for the analysis
261 AGESmaskROI = (clusid == 1);
262 n = size(Y,1);
263 ROI.mean = double(mean(Y(:,AGESmaskROI),2));
264 save('ROI.mat','ROI')
265
266 %% Significance Plot
267 figure(fig_num); % in case it doesn't already exist
268 if ((max(size(clusid))==0) || (min(pval.C)>pthresh))
269     close(fig_num);
270     disp(strcat({'No significance for '}, figtext));
271     fig_num = fig_num+1;
272     figure(fig_num);
273     close(fig_num);
274 else
275     lab = strcat({'Significance of '}, figtext);

```

```

276     SurfStatViewFig( pval, avsurf, lab, 'white', compact );
277     pos = get(fig_num, 'Position');
278     pos(1:2) = [50 (i-1)*250];
279     set(fig_num, 'Position', pos);
280     fig_num = fig_num+1;
281
282 % Percentage Difference Plot
283     figure(fig_num);
284     if 1
285         lab = strcat(figtext, {' difference with THR '}, units1);
286         SurfStatViewDataFigMasked( 100*(slm.coef(3,:)-slm.coef(2,:))./mY, ...
            avsurf, lab, 'white', pval, clim1, blank_nonsig, compact, cmap);
287         pos = get(fig_num, 'Position');
288         pos(1:2) = [200 (i-1)*250];
289         set(fig_num, 'Position', pos);
290     end
291 end
292
293 fig_num = fig_num + 1;
294
295 % Mean Difference Plot
296     figure(fig_num);
297     lab = strcat({'Mean '}, figtext, {' '}, units2);
298     SurfStatViewDataFig( meanY, avsurf, lab, 'white', compact, cmap );
299     SurfStatCollim(clim2);
300     pos = get(fig_num, 'Position');
301     pos(1:2) = [200*3 (i-1)*250];
302     set(fig_num, 'Position', pos);
303     fig_num = fig_num+1;
304 end

```

Appendix C

AGES General Linear Model Analysis Matlab Script

This Matlab script was written by Graham M Treece, adapted and commented by me for the AGES dataset.

```
1 % what sort of validation to do
2 cross_validate = true;
3 include_jsm = false;
4 include_shape = false;
5
6 do_pain = [0 0 0 1];
7 do_kandl = [1 0 0 0];
8 do_jsw = [0 1 0 0];
9 do_cbm = [0 0 1 0];
10
11 % do_kandl = [1 0 0];
12 % do_jsw = [0 1 0];
13 % do_cbm = [0 0 1];
14 % do_pain = [1 1 1];
15
16 % do_kandl = [1];
17 % do_jsw = [0];
18 % do_cbm = [1];
19 % do_pain = [1];
20
21 clear names x y h;
22
23 ls = {'k-' 'k:' 'k—' 'k-'};
24 lw = [1 1 1 2];
25 lc = [[0 0 0]; [0 0 0]; [0 0 0]; [0.6 0.6 0.6]];
26
27 % load data
28 load coeffs;
29
30 for n=1:length(do_cbm)
31     include_pain = (do_pain(n)==1);
32     include_kandl = (do_kandl(n)==1);
33     include_jsw = (do_jsw(n)==1);
34     include_cbm = (do_cbm(n)==1);
35
36     % load JSW Data and combine
37     if (include_jsm)
38         load jsw_roi;
39         [id ia ib] = intersect(id, str2num(char(ROI.id)));
40         age = age(ia);
41         height = height(ia);
42         JSW = JSW(ia);
43         KL = KL(ia);
44         OP = OP(ia);
45         replace = replace(ia);
46         sex = sex(ia);
47         weight = weight(ia);
48         pain = pain(ia);
49         m{1} = m{1}(ia);
50         m{2} = m{2}(ia);
```

```

51     m{3} = m{3}(ia);
52     m{4} = m{4}(ia);
53     m{5} = m{5}(ia);
54     m{6} = m{6}(ia);
55     mean_values = mean_values(ia,:);
56     meanJSM = ROI.mean_JSW(ib);
57     minJSM = ROI.min_JSW(ib);
58 end
59
60 % set up X and Y for mnrx
61 if (include_shape)
62     mnrx = [age strcmp(sex,{'male'})];% weight];
63     model = {'Constant'; 'Age'; 'Sex'; %; 'Weight'};
64     data_start = 3;
65 else
66     mnrx = [age strcmp(sex,{'male'}) height];% weight];
67     model = {'Constant'; 'Age'; 'Sex'; 'Height'; %; 'Weight'};
68     data_start = 3;
69 end
70 if (include_pain)
71     mnrx = [mnrx strcmp(pain,{'yes'})];
72     model = [model; {'Pain'}];
73 end
74 if (include_cbm)
75     mnrx = [mnrx mean_values(:,1)];% mean_values(:,3)];
76     model = [model; {'CTh'}];% 'ECTD' };
77     %mnrx = [mnrx mean_values(:,1)];
78     %model = [model; {'CTh'}];
79 end
80 if (include_jsm)
81     %mnrx = [mnrx meanJSM minJSM];
82     %model = [model; {'Mean JSM'; 'Min JSM'}];
83     mnrx = [mnrx minJSM];
84     model = [model; {'Min JSM'}];
85 end
86 if (include_kandl)
87     mnrx = [mnrx KL];% JSW OP];
88     model = [model; {'KL'}];% 'Min JSW'; 'OP'}];
89 end
90 if (include_jsw)
91     mnrx = [mnrx JSW];
92     model = [model; {'Min JSW'}];
93 end
94 if (include_shape)
95     mnrx = [mnrx m{1} m{2} m{3} m{4} m{5} m{6}];
96     model = [model; {'Shape 0'; 'Shape 1'; 'Shape 2'; 'Shape 3'; 'Shape ...
97         4'; 'Shape 5'}];
98 end
99 mnry = [strcmp(replace,{'yes'}) strcmp(replace,{'no'})];
100 pred = {'Hip replacement'};
101 cont = 2;
102 subjects = max(size(age));
103 name = '1';
104 for m=2:length(model)
105     name = sprintf('%s + %s', name, char(model(m)));
106 end
107 name2 = '1';
108 for m=2:data_start

```

```

108     name2 = sprintf('%s + %s', name2, char(model(m)));
109 end
110
111 % normalise these values
112 mnrx = mnrx-ones(subjects,1)*mean(mnrx);
113 sd = std(mnrx);
114 sd(1) = 5; % age is per 5 years, everything else is per SD
115 sd(2) = 1; % doesn't make sense dividing sex by SD
116 mnrx = mnrx./(ones(subjects,1)*sd);
117 glmY = strcmp(replace,{'yes'});
118 glmX = mnrx;
119
120 % cross-validation - run the model on all but one, then test on that one
121 disp(' ');
122 disp('_____');
123 gp = zeros(subjects,1);
124 if (cross_validate)
125     fprintf(1,'Cross-validating GLM ,,, 0');
126     for i = 1:subjects
127         fprintf(1,'\b\b\b%3i',i);
128         gX = glmX;
129         ind = [1:subjects]~i;
130         [gb gdev gstats] = glmfit(gX(ind,:), ...
131             glmY(ind,:), 'binomial', 'link', 'logit');
132         gp(i,:) = glmval(gb,gX(i,:), 'logit');
133     end;
134     fprintf(1,'\n');
135 else
136     [gb gdev gstats] = glmfit(glmX, glmY, 'binomial', 'link', 'logit');
137     gp = glmval(gb,glmX, 'logit');
138     gX = glmX;
139 end
140 [glm_b gdev gstats] = glmfit(gX, glmY, 'binomial', 'link', 'logit');
141 glm_p = gp;
142
143 % convert results to ROC curves
144 nr = 2001;
145 ind = mnry==1;
146 tp_glm = zeros(nr,1);
147 fp_glm = zeros(nr,1);
148 for i = 1:nr;
149     tp_glm(i) = sum(gp(~ind(:,cont))>((i-1)/(nr-1)))/sum(1-mnry(:,cont));
150     fp_glm(i) = sum(gp(ind(:,cont))>((i-1)/(nr-1)))/sum(mnry(:,cont));
151 end;
152 tp_glm(1) = 1;
153 fp_glm(1) = 1;
154 tp_glm(nr) = 0;
155 fp_glm(nr) = 0;
156
157 y(:,n) = fp_glm(:,1);
158 x(:,n) = tp_glm(:,1);
159 auc_glm = -sum(diff(fp_glm).*tp_glm(1:(nr-1),:));
160 names(n) = cellstr([name ' , AUC = ', num2str(auc_glm(1))]');
161
162 % odds ratios of model
163 disp(' ');
164 disp(name);
165 disp(' ');

```

```

165 disp(sprintf('Deviance: %.2f (%.2f including cross-validation)', ...
    gdev, -2*sum( glmY.*log(glm-p) + (1-glmY).*log(1-glm-p) ));
166 disp(sprintf('Degrees of Freedom: %i', size(mnrX,2)));
167 disp(' ');
168 se = gstats.se;
169 p = gstats.p;
170 disp(sprintf('\tOdds\t\t(range)\t\t\tp!=0\tCoeff'));
171 for i=1:size(gb,1); disp(sprintf('\t%.3f\t(%.3f to %.3f)\t%.5f\t %s', ...
    exp(gb(i)), exp(gb(i)-2*se(i)), exp(gb(i)+2*se(i)), p(i), ...
    model{i})); end
172
173 % odds ratios of individual terms
174 disp(' ');
175 disp(name2);
176 disp(' ');
177 disp(sprintf('\tOdds\t\t(range)\t\t\tp!=0\tCoeff'));
178 for i=data_start:size(gX,2);
179     gmdl = fitglm(gX(:, [1:(data_start-1) i]), ...
        glmY, 'linear', 'Distribution', 'binomial', 'Link', 'logit');
180     gb = gmdl.Coefficients.Estimate;
181     se = gmdl.Coefficients.SE;
182     p = gmdl.Coefficients.pValue;
183     disp(sprintf('\t%.3f\t(%.3f to %.3f)\t%.5f\t %s', ...
        exp(gb((data_start+1))), ...
        exp(gb((data_start+1))-2*se((data_start+1))), ...
        exp(gb((data_start+1))+2*se((data_start+1))), p((data_start+1)), ...
        model{i+1}));
184 end
185 end
186
187 figure(1);
188 hold off;
189 for n=1:length(do_cbm)
190     h(n) = plot(y(:,n), x(:,n), char(ls(n)), 'LineWidth', lw(n), 'Color', ...
        lc(n,:));
191     if (n==1) hold on; end
192 end
193 legend(h, names, 'Location', 'SouthEast');
194 xlabel('False positive rate', 'FontSize', 14);
195 ylabel('True positive rate', 'FontSize', 14);
196 title('Cross-validated ROC', 'FontSize', 14);
197 set(gcf, 'Color', [1 1 1]);
198 set(gca, 'FontSize', 14);
199 set(gcf, 'Position', [600 600 650 470]);

```

Appendix D

Image .wrl File Generation Matlab Script For 3D Printing

Matlab code written by Tristan Whitmarsh, adapted and commented by me to generate a .wrl image file.

```
1 load thick_cmaps;
2 C=thick_clim1;
3 meanY_percentage = 100*(slm.coef(3,:)-slm.coef(2,:))./mY;
4
5 for n = 1:5580
6     t = meanY_percentage(n); % Percentage changes
7     if t < C(1) % if smaller than min value then colour is
8         t = C(1); % min value (smaller than 0)
9     end
10    if t > C(2) % if bigger than max value then colour is
11        t = C(2); % max value (bigger than 0)
12    end
13
14    % values 0-70 but need values between 0-254 therefore converted
15
16    % equation to get to 0 from thickness values to a colour index
17    Ci= fix((t-C(1))/(C(2)-C(1))*size(cmap4,1))+1;
18
19    BL(n,:) = cmap4(Ci,:); % export to matlab file
20
21    if pval.C(n) > 0.05 % regions of significance (ignores
22        % values less than 0.05 and greys them out)
23        BL(n,:) = [0.7, 0.7, 0.7]; % colour choice 0.5 = grey, 0.7 = light
24        % grey, 1 = white
25    end
26
27 end
```

Appendix E

Shape Mode Changes

